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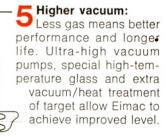
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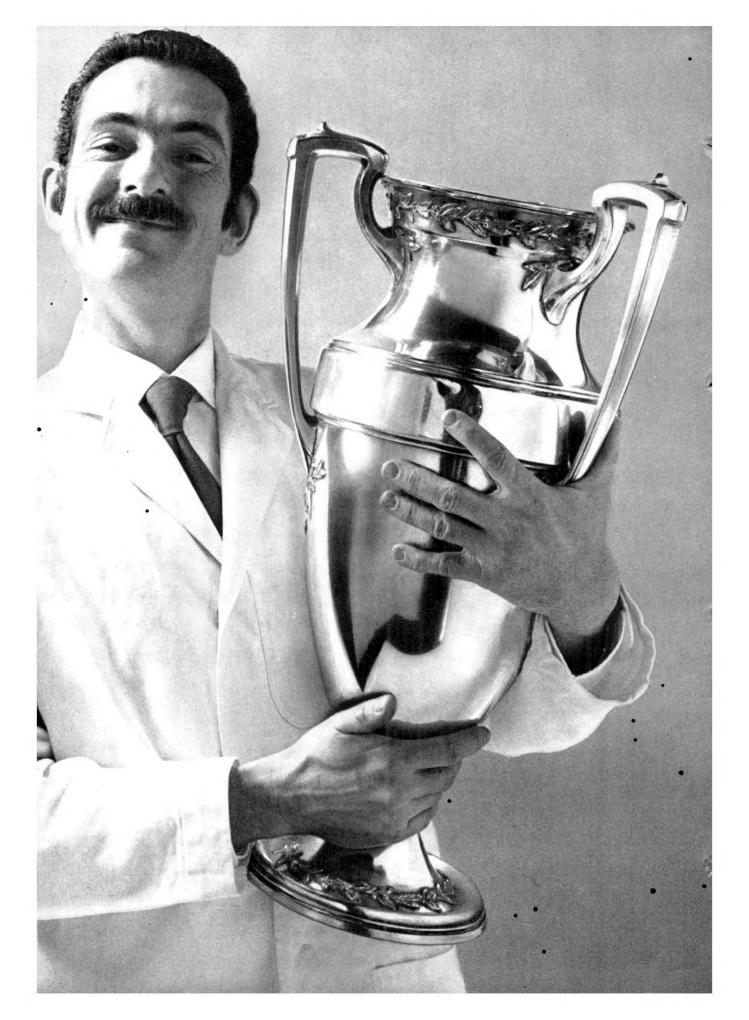
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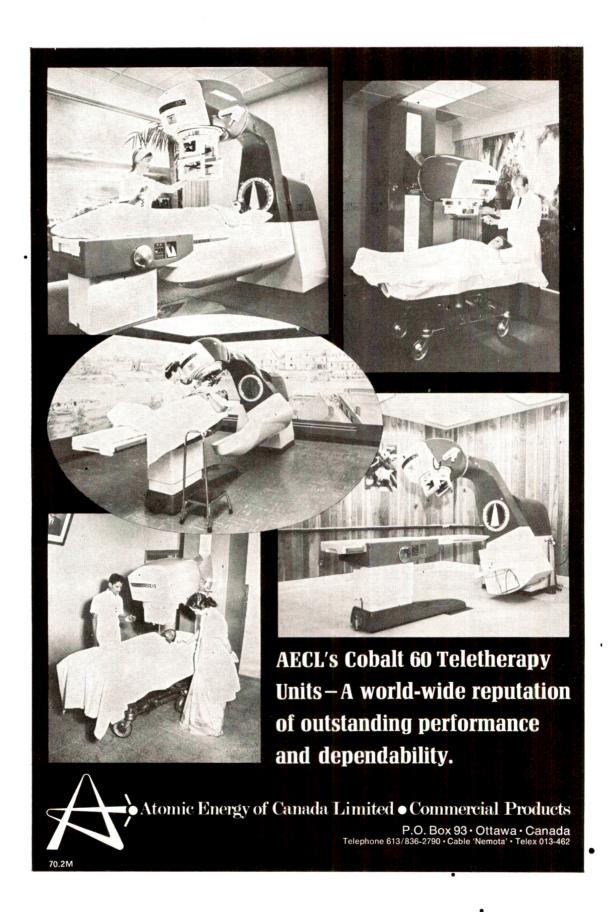
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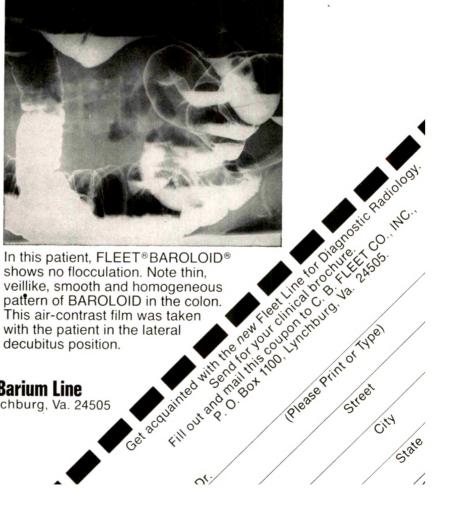
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\*Bryk, D. and Roska, J. C.: Radiology 92:832, Mar., 1969.



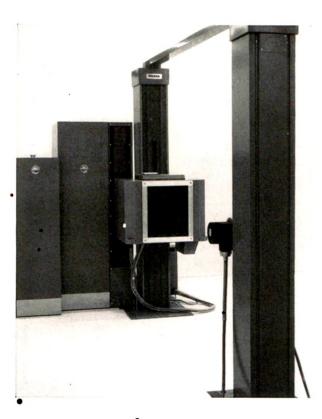
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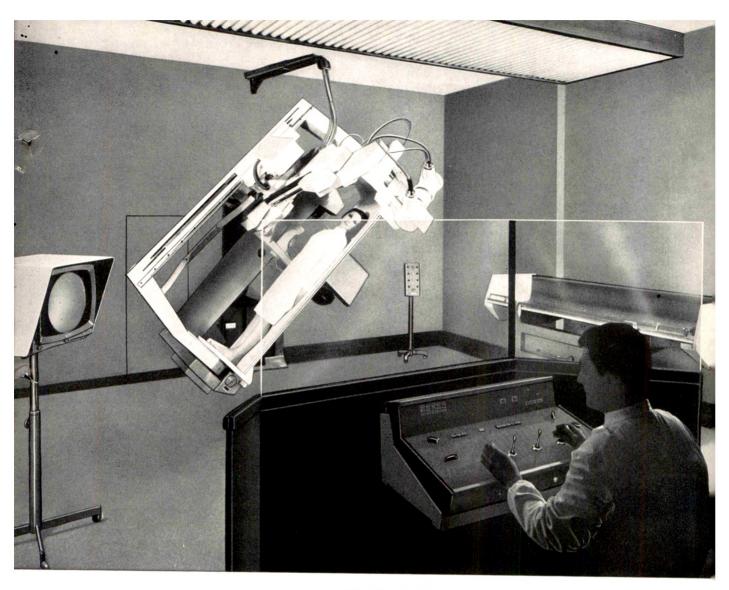
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## A COLONIC EVACUANT

## **Description:**

Each packet of CLYSODRAST contains 1.5 mg. of 4,4'- (diacetoxydiphenyl) - (pyridyl - 2) methane complexed with 2.5 Gm. of Tannic Acid, N.F., in a readily soluble form.

### Actions.

CLYSODRAST is a non-absorbable colonic evacuant which provides good cleansing of the colon when used as an enema. The tannic acid serves to solubilize the 4,4'-(diacetoxydiphenyl) - (pyridyl - 2) - methane as well as to inhibit the secretion of the secretory glands in the colonic mucosa. Tannic acid contained in CLYSODRAST is water-soluble and precipitates protein. Its astringent effect inhibits secretion of mucus in the walls of the large intestine.

### Indications:

CLYSODRAST (bisacodyl tannex) may be indicated for the preparation of patients for radiologic examinations of the colon, sigmoidoscopy and proctologic examinations.

### **Contraindications:**

CLYSODRAST is contraindicated in patients under the age of 10 because the possibility of absorption of tannic acid has not been adequately studied in this age group to warrant a conclusion of safety. CLYSODRAST is also contraindicated in cases with known or suspected extensive ulcerative lesions of the colon.

## Warning:

## Usage in Pregnancy

Safe use of CLYSODRAST has not been established with respect to the adverse effects upon fetal development. Therefore, it should not be used in women of child-bearing potential, particularly during early pregnancy, except where, in the judgment of the physician, the potential benefits outweigh the possible hazards.

## Precautions:

CLYSODRAST should be used with caution in a regimen where multiple enemas have been administered. Certain patients, because of age, debility, or underlying disease, require more gentle preparation than the routine castor oil and CLY-SODRAST (bisacodyl tannex) preparation. It is important that the instructions for preparation and administration be followed in detail, and that the recommended dosages not be exceeded.

### **Adverse Reactions:**

The following adverse reactions have been reported: Cramping, weakness, nausea and fainting.

## Dosage and Administration:

It is important that the entire medical history and condition of the patient be considered in decid-

ing the dosage regimen. Traumatizing procedures, such as repetition of enemas (with or without CLYSODRAST) should be kept at the minimum necessary to achieve the desired result.

3

## Cleansing Enema

Prepare the cleansing enema by dissolving the contents of one packet (2.5 Gm.) of CLYSODRAST in one liter of lukewarm water and administer.

### Barium Enema

Prepare the barium enema by dissolving the contents of one or not more than two packets (2.5 Gm. or 5.0 Gm.) of CLYSODRAST in one liter of barium suspension. If more than one liter of barium suspension is prepared, it is important that the concentration of CLYSODRAST (bisacodyl tannex) never exceed 0.5 percent (2 packets per liter).

The total dosage of CLYSODRAST for any one complete colonic examination, including the cleansing enema, should not exceed 7.5 Gm. (3 packets). No more than 10 Gm. (4 packets) of CLYSODRAST should be administered to any individual within a 72-hour period.

## Preparation of the Patient:

## General Procedure

On the day prior to examination, the patient is placed on a residue-free diet. Castor oil, one to two ounces, is administered approximately 16 hours before examination. On the day of examination, the CLYSODRAST cleansing enema is given (see "Dosage and Administration") and expelled. Results are inspected and if a considerable amount of fecal material is present in the toilet bowl, the enema may be repeated.

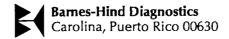
Routine Barium Enema — In addition to the general procedure outlined above, good evacuation of the barium sulfate enema may be obtained by adding CLYSODRAST to the suspension as described under "Dosage and Administration."

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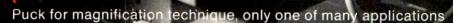
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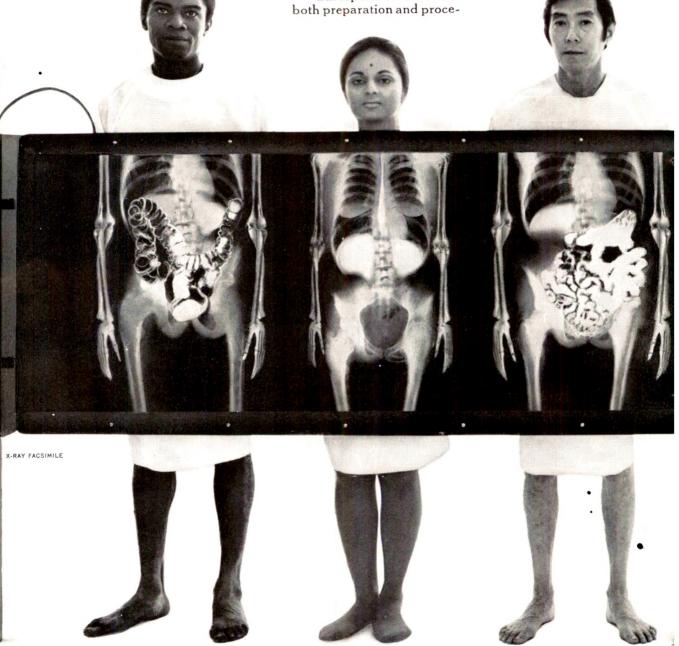
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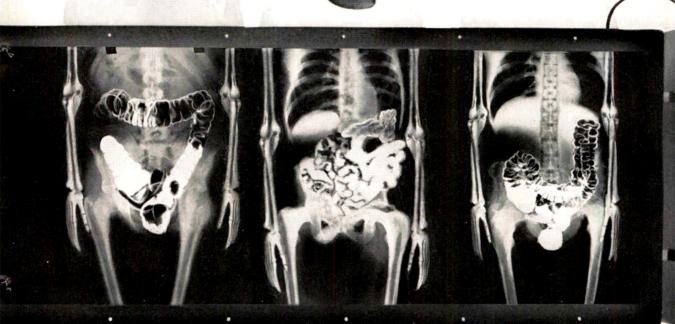
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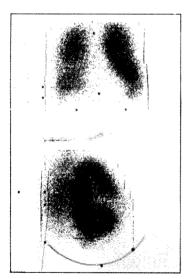
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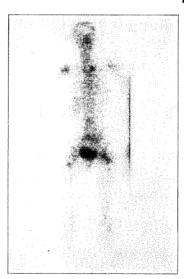
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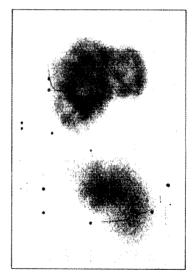
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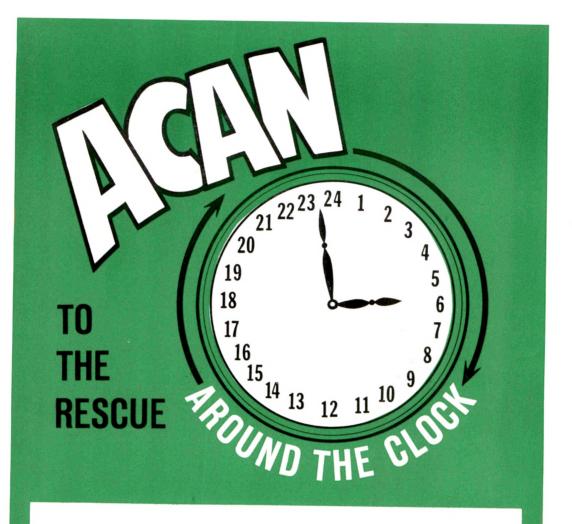
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Minified 5:1 Whole Body Bone Scan
Dose: 3 mCi Radionuclide: 87mSr
Post Injection Time: 4 hrs.
Scan Speed: 750 cm./min.
TOTAL SCAN PROCEDURE TIME:
25 min. (2 views)
Courtesy of Univ. of fowa, Dept. of Radiology
Section of Nuclear Medicine, Iowa City, Iowa



AP & Right Lateral 84FD
Minified 2:1 Liver Scan
Dose 1.5 mCi Radionuclide: 99mTc (SC)
Scan Speed: 300 cm./min.
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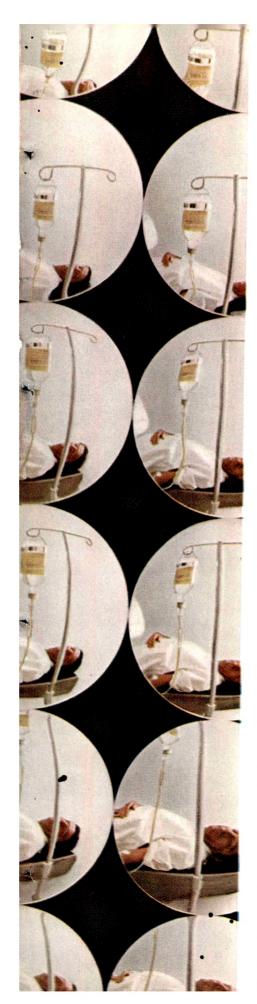
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#### Better visualization

Improvement over regular I.V. pyelography was shown specifically in 89.5% of 180 cases by 8 of the 18 investigators.<sup>1</sup>

#### Adverse reactions

Adverse reactions were generally mild and occurred in 6.7% of the cases. The most frequent reactions were nausea and urticaria (see brief summary on next page). (All meglumine diatrizoate solutions used were equivalent to 30% concentration.)

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1. Data on file at The Squibb Institute for Medical Research. See next page for brief summary.

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# RENO-M-DIP

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Reno-M-DIP<sup>TM</sup> (Meglumine Diatrizoate Injection U.S.P.) or drip infusion pyelography provides a sterile, aqueous solution of 30% meglumine diatrizoate which contains approximately 14% (42.3 grams per 300 cc.) bound iodine and 0.04% disodium edetate as a sequestering agent. The solution contains approximately 0.054 mg. (0.002 nEq.) sodium per cc. (16.2 mg. per 300 cc.).

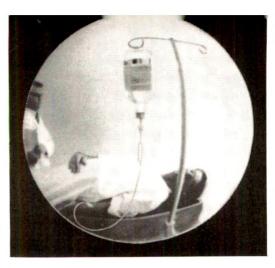
Contraindications: Contraindicated in persons hypersensitive to salts of diatrizoic acid. Urography is contraindicated in patients with anuria.

Narnings: A definite risk exists with the use of contrast agents in excretion urography in patients with multiple nyeloma. There has been anuria with progressive urenia, renal failure and death. This risk of the procedure n these patients is not a contraindication; however, partial dehydration in preparation for study is not recommended since it may predispose for precipitation of nyeloma protein in renal tubules. No therapy, including dialysis, has been successful in reversing this effect. Myeloma should be considered in persons over 40 beore undertaking urographic procedures.

In cases of known or suspected pheochromocytoma, if the physician feels that the possible benefits outweigh the considered risks, radiopaque materials should be administered with extreme caution; however, an absolute minimum of material should be injected, the blood pressure should be assessed throughout the procedure, and measures for treating a hypertensive crisis should be available.

Contrast media may promote sickling in homozygous individuals when injected I.V. or intra-arterially. Although a history of sensitivity to iodine *per se* or to other contrast media is not an absolute contraindication, administration of meglumine diatrizoate requires extreme caution in such cases. Meglumine diatrizoate should be used in pregnant patients only when the physician deems its use essential to the welfare of the patient since safe use during pregnancy has not been established. Perform thyroid function tests prior to administration of meglumine diatrizoate since iodine-containing contrast agents may alter the test results. Perform urography with extreme caution in persons with severe concomitant hepatic and renal disease.

Precautions: Diagnostic procedures involving use of contrast agents should be performed under the direction of personnel with prerequisite training and a thorough knowledge of the particular procedure. Appropriate facilities should be available for coping with situations which may arise as a result of the procedure and for emergency treatment of severe reactions to the contrast agent itself; competent personnel and emergency facilities should be available for at least 30 to 60 minutes after I.V. administration since delayed reactions have been known to occur. These severe life-threatening reactions suggest hypersen-



sitivity to the contrast agent. A personal or family history of asthma or allergy or a history of a previous reaction to a contrast agent warrants special attention and may predict more accurately than pretesting the likelihood of a reaction although not the type nor severity of the reaction in the individual. The value of any pretest is questionable. The pretest most performed is the slow injection of 0.5-1.0 cc. of the preparation which may be given through the needle to be used for the full dose. If no reaction occurs within 15 minutes, the full dose may be given; however, this does not preclude the possibility of reaction. Should the test dose produce an untoward response, the necessity for continuing the examination should be reevaluated. If deemed essential, examination should proceed with all possible caution. In rare instances, reaction to the test dose may be extremely severe; therefore, close observation and facilities for emergency treatment are indicated.

Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by urographic agents; therefore, if known or suspected hepatic or biliary disorder exists, administration of meglumine diatrizoate should be postponed following the ingestion of cholecystographic agents. Consider the functional ability of the kidneys before injecting meglumine diatrizoate.

The recommended rate of infusion should not be exceeded. The diuretic effect of the drip infusion procedure may hinder an assessment of residual urine in the bladder. Adequate visualization may be difficult or impossible in uremic patients or others with severely impaired renal function (see Contraindications).

Adverse Reactions: Reactions most frequently encountered with drip infusion pyelography are nausea and urticaria. Chills, metallic taste, vomiting, dizziness, a rise or fall in blood pressure, itching, flushing, or generalized feeling of warmth, sneezing, etc. may occur and, rarely, may be severe enough to require discontinuation of dosage. Severe reactions which may require emergency measures (see Precautions) are a possibility and include cardiovascular reaction characterized by peripheral vasodilatation with hypotension and reflex tachycardia, dyspnea, confusion, and cyanosis progressing to unconsciousness. An allergic-like reaction ranging from rhinitis or angioneurotic edema to laryngeal or bronchial spasm or anaphylactoid shock may occur. Temporary renal shutdown or other nephropathy may occur. Intravenous injection of meglumine diatrizoate in a more concentrated formulation has produced a few instances of a burning or stinging sensation and of venospasm or venous pain.

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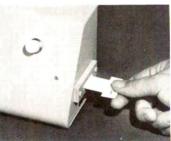
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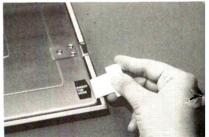
1. Type or write pen or pencil) padata on special label.



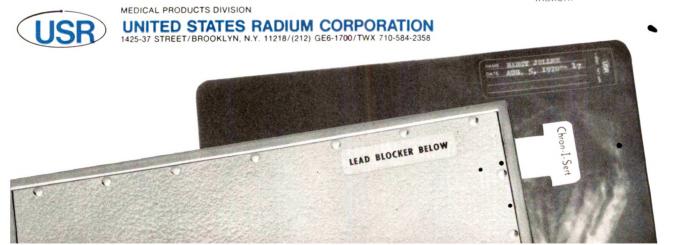
Step 2. Mount label on Chron-I-Sert insertion strip, and send into x-ray room with patient.



Step 3. Insert Chron-l-Sert (label on strip) into Exciter for a few moments and then withdraw.



Step 4. Insert Chron-I-Sert into Chron-I-Sette slot.Remove in 3 seconds. Patient-film identification is complete—proceed with radiographic examination.



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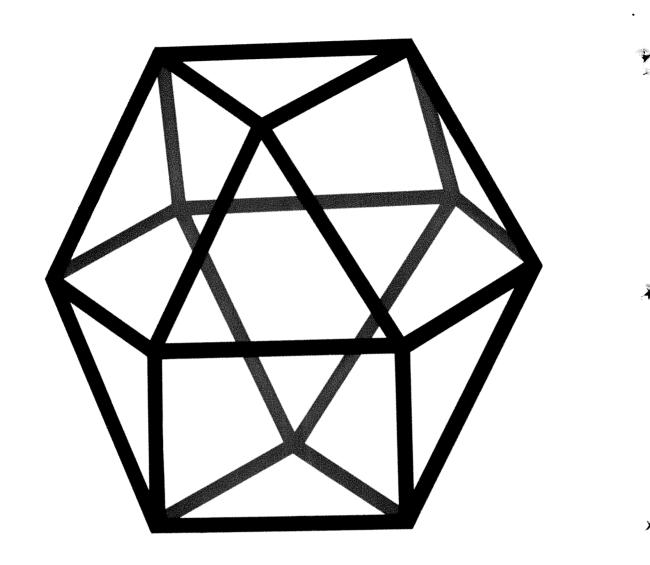
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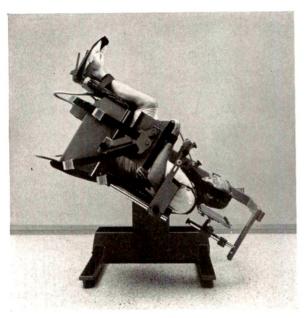
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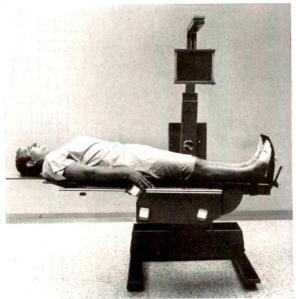
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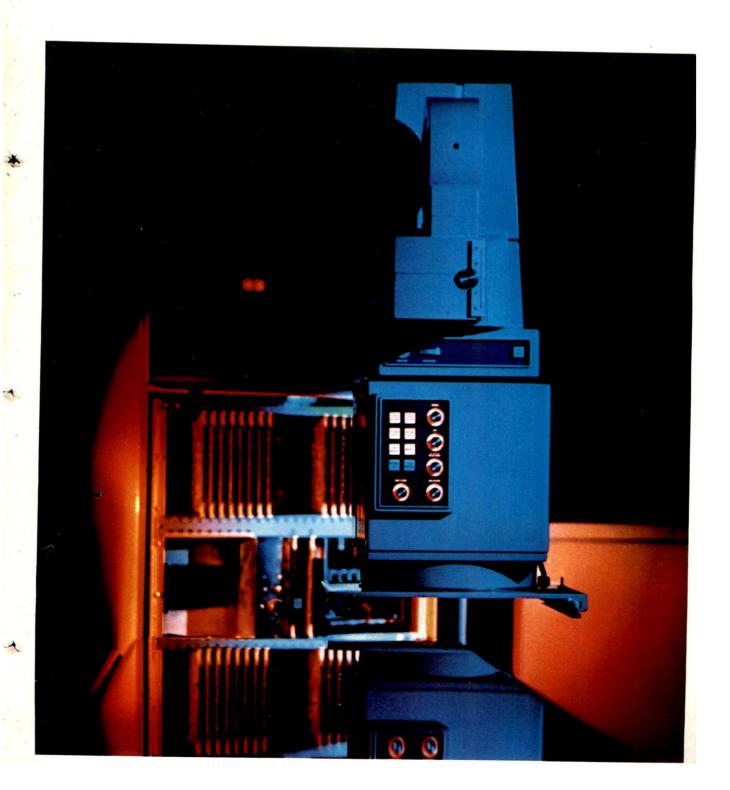
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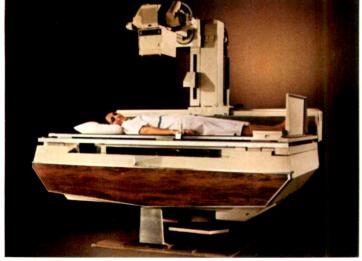
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FERNANDO G. BLOEDORN, M.D.

# THE AMERICAN JOURNAL OF ROENTGENOLOGY

# RADIUM THERAPY AND NUCLEAR MEDICINE

Vol. III

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JANUARY, 1971

No. 1

# E PLURIBUS UNUM\* THE PRESIDENT'S ADDRESS, 1970

By FERNANDO G. BLOEDORN, M.D. BOSTON, MASSACHUSETTS

THE American Radium Society has been associated since its origin with the remarkable advancements made in the therapy of cancer. We can note with pride that many of our members contributed in making progress possible. However, we should also note that in spite of the improvements made in its cure rate, cancer remains a primary problem confronting the medical profession in the United States. Consistent with the tradition of our Society our members are, and should continue to be, engaged in the search for better solutions to this challenging problem. It is my conviction, that we can better serve the ideals of our Founders and make greater therapeutic gains by unifying our efforts and by freeing ourselves from the confining boundaries of specialties and institutions, in order to improve the delivery of medical care. An immediate improvement in the cure rate of cancer is possible if we can succeed in developing a better organized combined therapy and a regional medical system capable of delivering the best therapy to all patients.

Considering the magnitude of the task, the clinical and research forces devoted to this effort are small and deficiently organized, especially when compared with other medical specialties. The reasons are multiple: history, geography, economics. Probably the most outstanding reason is the historic development of our segment of the medical profession. Perhaps it will help us to understand our present problems if we re-live the highlights of the development of cancer therapy in this country.

This development can be traced by eras represented by outstanding men with original ideas and great energy. There is considerable overlap between eras, perhaps as a result of some men who were undecided, too conservative, or ignorant of new advancements, and, furthermore, because many of the men who represented one period set the foundations for the following period.

The first era is one of disorganized efforts—each man by himself with a paucity of knowledge and resources, armed only with his daring, and frustrated by the failure of

Presented at the Fifty-second Annual Meeting of the American Radium Society, Coronado Island, San Diego, California, March 1-5, 1970.

his attempts. It began in the pre-anesthetic age when a bold "surgeon" made some therapeutic attempt in desperate situations. This era extended from the use of the red hot iron rod to the well-regulated, aseptic surgical act. At the beginning, it probably consisted of the elimination of exophytic masses in the breast and of other extruding malignancies, or the quick amputation of a limb hopelessly involved by tumor. The landmark for the end of this era is the work and concepts of Halsted and his development of a rational surgical approach to the treatment of breast cancer.

This was followed by a period of a systematic surgical method in cancer therapy aided by satisfactory anesthesia. Now surgeons can plan to remove tissues and organs invaded by malignant tumors. They develop and apply new techniques with the hope that some cures will crown their efforts.

This period yielded slowly to the next, with considerable overlapping of time. The new period initiated the foundation of modern cancer therapy with original rudimentary attempts at combined therapy. Surgeons and gynecologists, impressed by the experiences of their European colleagues, began experimenting enthusiastically with radium, some of it prepared by Madame Curie. Radium therapy was born without the clear limits of a specialty. Its early application to the treatment of cancer by surgeons and clinicians strengthened the foundations for radiotherapy. Radiation was used in hopeless, inoperable cases or occasionally combined with surgery. H. H. Janeway is the outstanding name of this period. His desperate efforts to develop a system for the proper usage of radium in the treatment of tumors were enhanced by his faith in the new modality of treatment and his hope of finding a solution to his own devastating problem—an incurable tumor of the jaw. It was very unfortunate for him and the specialty that his hope was not realized. Other outstanding names of the same era were R. Abbe, who used interstitial radium for the first time in the treatment of cancer in the United States, H. Kelly, who started to apply radium systematically to pelvic malignancies, and two of our Founders, J. T. Case and H. K. Pancoast, who pioneered in the use of roentgen rays in therapy and diagnosis.

With the development of new knowledge and techniques, a master specialist to solve all the problems related to cancer patients was needed. This concept gave birth to the oncologist, who acquired his main background in surgical training with additional training in pathology, diagnostic procedures, and radiotherapy. The Memorial Hospital in New York became the primary center for training in this specialty. The approach was multidisciplinary indeed; however, all the disciplines were crowded in the same individual. The system produced outstanding men and a marked improvement in the therapy of cancer. I cannot fail to mention George Pack as the notable man of this era. However, before the first generation of oncologists aged into retirement, it became evident that the amount of knowledge necessary for a man to efficiently solve all the problems of his cancer patients was overwhelming.

This last accumulation of information and new procedures, combined with the example of European centers, signaled a new age in the therapy of cancer. The characteristic of this new era is the "confined specialist," which began with the surgeon and the radiologist interested in cancer treatment. As new information, techniques and equipment increased, the limits of the specialties narrowed: the Head and Neck, Gynecology, Urology, and Thoracic Cancer surgeons; and the radiotherapist; radiophysicist; and radiobiologist emerged. More recently the field has benefited from a new group of specialists, the chemotherapists, who have contributed to our understanding of malignant processes and their treatment. This proliferation of subspecialties brought with it a contest for supremacy, because each special-

## NEGATIVE PIONS: THEIR POSSIBLE USE IN **RADIOTHERAPY\***

By V. P. BOND UPTON, LONG ISLAND, NEW YORK

THE possible advantages of negative  $\pi$  mesons in radiotherapy have been outlined in an initial paper by Fowler and Perkins in 1961,14 and in a number of subsequent publications by these and other authors.  $^{1}_{1,6,15-19,28,30}$  Beams of negative  $\pi$ mesons to date have been of low intensity, adequate for physical and dosimetric studies, but marginal for radiobiologic studies.

The purpose of the present paper is to review the current status of the physics, dosimetry, and radiobiology of negative  $\pi$  mesons in order to assess their potential usefulness in radiotherapy.

With currently available approaches to radiotherapy, it is necessary to irradiate normal tissue with the same quality radiation as delivered to the tumor, and often large amounts of normal tissue are exposed to essentially the same dose and dose rate as is the tumor. Thus the differential effect on tumor versus at least some normal tissues must depend to an appreciable degree on differences in biologic factors and responses between tumor and exposed normal tissues; e.g., absolute radiosensitivity, repair\* or recovery capability, oxygen tension.

Should it be possible to expose the tumor tissue to radiation of a quality (LET†) that is significantly different from that delivered to normal tissue, the possibility would exist of employing physical as well

\* Repair here is used to denote repair of sublethal cellular radiation in ury. Recovery denotes over-all tissue restitution, and may include repair, cell division and other factors.

as biologic factors to enhance the probability of therapeutic success. This possibility exists with negative  $\pi$  mesons.

A limitation in radiation therapy that may be determining in at least some types of tumors involves so-called "hypoxic cells." Most tumors contain foci of poorly oxygenated cells, presumably as a result of impaired blood supply. It is a well established fact in radiation biology that hypoxic cells exposed to x or gamma radiations are protected by a dose factor of as much as 3; i.e., three times the radiation dose may be required to inflict a given amount of damage on a population of hypoxic cells as would be required if the cells were well oxygenated. If densely ionizing radiations (such as alpha particles in the several MeV energy range, or recoil protons from elastic collisions of fast neutrons with hydrogen nuclei) are used, however, the factor of protection afforded hypoxic cells is considerably less than 3. Thus, densely ionizing radiations would potentially ameliorate the problem of hypoxic tumor cells.

#### I. PHYSICAL CHARACTERISTICS OF THE $\pi^-$ BEAM

A. PHYSICAL INTERACTIONS: ENERGY DEPOSITION IN TISSUE

The negative  $\pi$  meson has a mass 273 times that of the electron, or approximately 15 per cent of that of the proton. Along most of the path of a  $\pi$  meson in matter, it behaves much like an electron as regards rate of energy loss (or dE/dx). Near the end of its range, the slowed down meson is

<sup>†</sup> Linear Energy Transfer. Refers to energy absorbed per unit track; is the same as rate of energy loss or dE/dx under some conditions.

<sup>\*</sup> Presented at the Fifty-second Annual Meeting of the American Radium Society, Coronado Island, San Diego, California, March

Part of Symposium: High LET Radiation. Moderator, Michel Ter-Pogossian, Ph.D.

Modified after the report of the Ad Hoc Pion Review Committee convened by the Division of Biology and Medicine of the U. S. Atomic Energy Commission. The Committee, consisting of F. Bloedorn, V. Bond (Chairman), J. Brennan, G. Fletcher, H. Kaplan, M. Kligerman, J. Laughlin, H. Rossi, H. Suit, M. Ter-Pogossian, W. Sinclair and C. Von Essen, submitted its report to the AEC on May 1, 1969. From the Brookhaven National Laboratory, Upton, Long Island, New York.

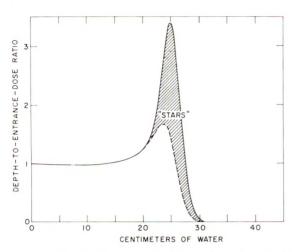


Fig. 1. Depth-dose curve in tissue for a beam of pure π<sup>-</sup> mesons. Momentum 190 MeV/c ±5 per cent. (S. Curtis, calculated.<sup>10</sup>)

captured in atomic orbits to form a "mesic atom," which then disintegrates.

In tissue, nuclear reactions with negative  $\pi$  mesons occur at the end of the particle track, principally with carbon and oxygen. The cross section for interaction increases linearly with Z. Interactions with oxygen may be taken as typical, and data are given 9,10,23,24 for a beam of negative  $\pi$ mesons with an energy of 96 MeV, a momentum of 190 Mev/c, a momentum spread of  $\pm 5$  per cent, and a range in tissue of approximately 25.5 cm. Of the rest mass of 140 MeV, approximately 96 MeV is converted to energy of emitted particles, and approximately 44 MeV goes into nuclear excitation and the binding energy of the nucleus. Particles produced at the end of the particle track and their approximate average energies are as follows: protons (15 MeV); alpha particles (8 MeV); Z  $\geq 3$  (4.4 MeV); and neutrons (69 MeV). The average numbers of these particles per star are in approximately the following proportion: protons, 0.95; alpha particles, 0.99;  $Z \ge 3$ , 0.78; and neutrons, 2.7. The energy spectrum of each type of particle covers a wide range. Recoil particles from nuclear interactions must also be taken into account, since the energy and range are appreciable. Some 50 per cent of the recoils have ranges of 4 microns or more in tissue.

A beam of negative  $\pi$  mesons thus, by undergoing dE/dx losses much as do beams of other charged particles, produces a Bragg curve in tissue or other matter. In addition, because of nuclear distintegrations confined essentially entirely to the end of the range of the negative  $\pi$  mesons, additional energy in the form of high LET radiation is liberated in the region of the "peak" of the Bragg curve of the negative  $\pi$  mesons. Such a curve, showing the primary Bragg peak of the negative  $\pi$  mesons and the added energy from star formation at the end of the range, is shown in Figure 1.9,10 The curve is for a pre negative  $\pi$  meson beam with a momentum of 190 MeV/c, and a momentum spread of 5 per cent. The peak to plateau dose ratio is approximately 3.4 to I, and the full width at half maximum is about 4 cm. These values will vary with the energy spread of the beam.

#### B. RADIATION QUALITY

The plateau region of the depth-dose curve results mainly from dE/dx losses of the negative pions. The LET is thus quite low, similar to that of electron beams.

Calculations and some measurements are available on the quality of radiation in the peak region of the depth-dose curve. 9,10,23,24 These values are shown in Figure 2 for a beam contaminated with electrons and muons. Some data on LET and Y spectra

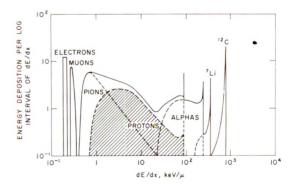


Fig. 2. Plot showing approximate LET distributions for a contaminated beam of π<sup>-</sup> mesons stopped in tissue. (S. Curtis, calculated.<sup>9.10</sup>)

obtained<sup>22</sup> with a Rossi type proportional counter are available, and the quality as measured experimentally agrees substantially with that predicted by calculation and shown in Figure 2. The peak region of the curve consists of radiations of widely varying LET. Residual negative pions in the peak region are, of course, very low LET. All higher LET components are born within the peak region. Protons vary widely in energy and in LET; the range is relatively short, and thus essentially all of their energy is deposited in the peak region. Alpha rays and higher Z nuclei constitute very high LET radiations of short range in tissue. Fast neutrons are born within the peak region, and have a wide energy spectrum. The mean free path extends beyond the peak region.

#### II. RADIOBIOLOGY OF THE $\pi^-$ BEAM

#### A. RBE\*; REPAIR OF SUBLETHAL CELL DAMAGE

The plateau portion of the negative pion beam is of very low LET, and the RBE is approximately 1.0. A sizable portion of the dose in the peak region of the  $\pi^-$  depth-dose curve is contributed by relatively high LET radiation, and thus the RBE of radiations in the peak region will be higher than that of the plateau. Direct measurements of the RBE in different regions of the depth-dose curve for  $\pi^-$  pions, determined for different doses and dose rates, will be presented below. However, numerical values for the RBE of high LET radiations usually vary considerably with absolute dose (or degree of biologic effect) and with dose rate (or fractionation pattern) employed in the determinations. These variations are of considerable importance, not only in comparing the RBE values for the  $\pi^-$  beam with those for other high LET sources, but in determining which values are applicable to different therapeutic regimens. Thus the nature of and reasons for the variation of RBE with dose and dose rate will be re-

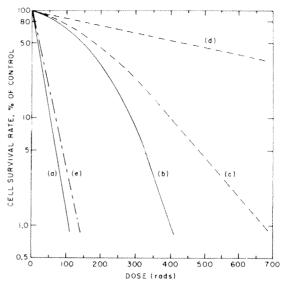


Fig. 3. Effect of protraction on cell survival rates following exposure to high and low LET radiations (schematic).

viewed briefly before experimental data obtained with the  $\pi^-$  beam are discussed.

Cellular dose-effect curves for high and low radiation, shown in Figure 3, are schematic, and are representative of the work of a number of individuals. 2,3,5,11,12 Curves a and b are for high and low LET radiations, respectively, both delivered at high dose rates (>10 rads/min.). Curve c is for low LET radiation delivered at low dose rates (of the order of 10 rads/hr.), or in fractions separated in time by several hours or more. Curve d is a hypothetical curve that may represent the extreme of what might be achieved with low LET radiation at extremely low dose rates or in repeated. very small fractions of dose. Curve e is for high LET radiation, delivered at low dose rates.

Distributing the dose in time, either by lowering the dose rate or delivering the dose in fractions separated by a time period of a few hours or more, increases the RBE because of differential rates of cellular recovery from sublethal damage inflicted by high and low LET radiation. With high LET radiation (compare curve a for a high dose rate, with curve e for low dose rate), the distribution of dose in time makes little

<sup>\*</sup> Relative Biologic Effectiveness. The inverse ratio of the dose of an unknown (usually high LET) radiation to that of a standard x or y radiation, required to produce the same degree of the same biologic effect.

Table I rbe of  $m{ au}^-$  mesons; peak of the depth-dose distribution

Effect Studied	Dose Rate* (rads/hr.)	RBE		: 
		Exponential Value	Value Adjusted to Same (high) Dose Rate	Reference
Vicia faba, abnormal anaphases	5-10	2.4	2.0	Richman et al.29
Vicia faba, 10 day growth	30	3	2.0	Raju and Richman <sup>25,26</sup>
Yeast, reverse mutations	25-30	1.5	1.5†	Raju and Richman 25.25
Ascites tumor cells, survival	5-10	5	3.0	Feola et al.18
Ascites tumor cells, survival Ascites tumor cells, polyploidy	25–30	5	2.5	Feola et al.13
induction	ζ-10	2.5	2.5	Loughman et al.21
Human kidney cells, frozen,	30	2	1.6	Barendsen et al.2.3
survival	25-30	~2	2.0†	Burki et al.8

\* Exposures with both \* mesons and the "standard" radiation carried out at this dose rate.

† Effects believed to be independent of dose rate under the conditions used.

RBE = Relative Biologic Effectiveness.

difference and curve e virtually superimposes on a. This denotes a lack of repair of sublethal cellular damage during or between the periods of exposures. With low LET radiation, however, considerable recovery of sublethal cellular damage occurs with low dose rate, or in the several hour intervals between fractions, so that additional radiation is required with fractionation or low dose rate to reduce the population to a given level of survival (compare curve b with curve c).

The net effect of dose rate or fractionation, therefore, is to increase the RBE of the high LET radiation.\* The maximum increase in RBE by virtue of lowered dose rate or fractionation is difficult to determine because of complicating factors (synchronization, cell death, cell division) that enter with the use of extended exposure times; however, it may be as high as a factor of 3 or 4 if very high and very low LET radiations are used (compare curves d and e). The differential is lower if radiations of intermediate LET are compared.

Experimental RBE values determined

in the peak portion of the  $\pi^-$  beam, with the dose ranges and dose rates employed. are given in Table 1. Differences in values may be due in large part to changes in effectiveness/rad with dose rate of the low LET comparison radiation. 5,82 These biologic experiments using  $\pi^-$  beams have been accomplished under considerably less than optimal conditions, as was well appreciated and pointed out by the authors. 8,18,21,25-27,29 The available beams are of low intensity and are significantly contaminated with electrons. It frequently has been difficult to ensure uniform dose deposition in the biologic specimen studied, either in depth (along the beam axis) or laterally. Also, the LET of the peak portion of the beam is a function of momentum spread of the beam.

In order to compare the experimental RBE values in Table 1 (peak portion of  $\pi^-$  curve) with those of other radiations, particularly fast neutrons, it is necessary to consider dose rate and, of course, the biologic effect studied. Attempts at precise extrapolation of results from one to other dose rates are not warranted; however, the results of a very approximate "normalization" are shown in Column 4 of Table 1. It

<sup>\*</sup> More accurately, to decrease the RBE of the low LET radiation. However, the low LET radiation is the standard by definition and this convention will be followed here.

appears reasonable that the RBE of  $\pi^-$  mesons (peak of curve) for cell survival at high dose rates (corresponding to curves a and b, Fig. 3) would be approximately the same as that of fast neutrons, *i.e.*, approximately 2. At low dose rates or with fractionation (corresponding to curves a and c, Fig. 3), the RBE would be expected to be at least double this value, or 4 or more.<sup>4</sup>

#### B. OXYGEN ENHANCEMENT RATIO (OER)\*

Because of the relatively high LET radiation in the peak portion of the  $\pi^-$  depthdose curve, the OER will be lower than in the plateau region (Fig. 4). The maximum OER obtainable particularly with low LET radiation (and thus in the plateau region of the curve) is of the order of 2.5 to 3.0. The minimum obtainable with very high LET radiation approaches 1.0.

Experimental difficulties similar to those outlined above for RBE determinations apply to OER determinations as well. The OER also varies with dose rate (less so than does the RBE): the lower the dose rate, the lower the OER. The results of several experiments<sup>25,27</sup> indicate that the OER for the peak portion of the  $\pi^-$  curve probably is of the order of 1.5 to 1.8, comparable to that for fast neutrons.

Calculations have been made of the OER to be expected in the peak region of the  $\pi^$ depth-dose curve, using biologic data obtained by the "track segment" approach involving rather narrow intervals of LET, together with calculated values for the LET distribution in the peak region of the curve. 10 The difficulties in this approach are recognized from experience with beams of fast neutrons, in which values for the OER calculated by this method have not been in good agreement with measured values; nonetheless, relative values should be accurate. One calculation,10 in which the recoils were treated separately, yielded an OER of approximately 1.8 to 2.2 over the

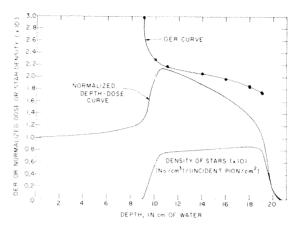


Fig. 4. OER (Oxygen Enhancement Ratio) in peak region of  $\pi^-$  depth-dose curve (S. Curtis, calculated.<sup>9,10</sup>)

bulk of the peak region of the depth-ionization curve.

## III. COMPARATIVE ADVANTAGES OF THE $\pi^-$ BEAM FOR RADIATION THERAPY

A. COMPARATIVE DEPTH-DOSE PATTERNS; SINGLE-AXIS AND MULTIPORT

The "peak" region of the ionizationdepth curve shown in Figure 1 is too narrow to accommodate most tumors; however, the peak region can be widened by increasing the momentum spread of the beam. The results32 of such an approach are shown in the lower left-hand panel of Figure 5 (the upper left panel represents the assumed energy distribution of pions in the beam, the upper right panel shows the resulting range distribution of the negative  $\pi$  mesons and the lower right panel shows the isodose contours corresponding to the central axis depth-dose curve shown in the lower left panel). It is seen (lower left-hand panel) that a sizable contribution to the total dose in the peak region, even with the peak spread out to some 10 cm. to accommodate a sizable tumor, comes from relatively high LET particles resulting from star formation. Also, the isodose contours in the lower right figure show that there is very lateral scatter, and virtually no exit dose.

The depth-dose pattern shown in the lower left-hand panel of Figure 6, achiev-

<sup>\*</sup> Oxygen Enhancement Ratio. The ratio of the dose of radiation delivered under hypoxic or anoxic conditions to that of the same degree of the same biologic effect.

#### T STOPPING IN H,O

30 MeV ENERGY DEPOSIT/STAR 26 % ΔΡ/Ρ

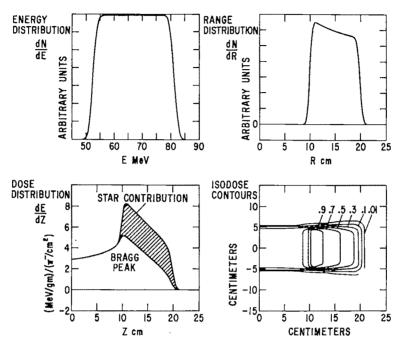


Fig. 5. Calculated energy, range, central axis depth-dose and isodose contours, relating to a beam of pure  $\pi^-$  mesons stopping in water. Momentum spread  $\pm 26$  per cent. (A. Thiessen, calculated.<sup>32</sup>)

able by placing a collimator of trapezoidal cross section at the momentum slit of the beam, is significantly more attractive than that shown in Figure 5. Figure 6 serves to illustrate the important point that with the beam of charged mesons one has considerable latitude in shaping the beam to a particular tumor in a particular location, by means of selective collimation, beam optics, or other means.

The curves in Figure 1  $^{9,10}$  and in Figures 5 and  $6^{32}$  are for beams of pure negative  $\pi$  mesons, essentially free from contamination by electrons or other charged particles. For a given absorbed dose to a tumor at some 10 cm. in depth, the skin and subcutaneous tissues would receive of the order of one-fourth or less absorbed dose with the  $\pi^-$  beam than with either  $Co^{60}$  or fast neutron irradiation.

An additional important factor is the relative sharpness of lateral cut-off of the

beams due to "penumbra," scattering in tissue, or other factors. The  $\pi^-$  beam will be much better in this respect than either the Co<sup>60</sup> or neutron beam; however, the extent achievable will depend on the degree of collimation that can be obtained in practice.

Multiport exposures are usually employed where feasible, and it is therefore important to compare beams under these conditions. Comparative 4 port isodose curves\* for Co<sup>60</sup> gamma rays, and  $\pi^-$ mesons are shown in Figures 7 and 8. (The situations depicted are schematic only, and are not intended to represent any real treatment plan.) It is apparent that under these circumstances, for a given absorbed dose to the tumor, the dose to tissues remote from the tumor is relatively small with  $\pi^-$  mes-

<sup>\*</sup> Curves were developed by M. Kligerman and associates: 

π⁻ curves were calculated from the data of A. Thiessen showsin Figures 5 and 6.22

#### T STOPPING IN HO

30 MeV ENERGY DEPOSIT/STAR 26 % AP/P

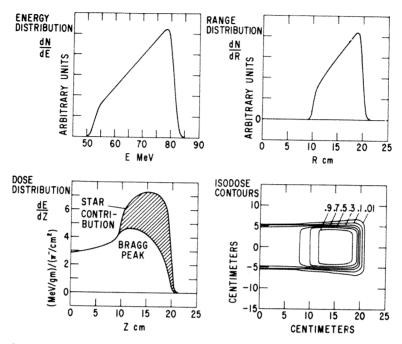


Fig. 6. Calculated energy, range, central axis depth-dose, and isodose contours for pure  $\pi^-$  mesons stopped in tissue. Beam has been "shaped" by means of a trapezoidal collimator. (A. Thiessen, calculated.<sup>32</sup>)

ons. The differential is much less striking for tissues close to the tumor.

An additional consideration must be taken into account in comparing multiport exposure patterns for different beams, namely, the mobility and location of the source relative to the patient. The conventional cobalt 60 therapy machine is relatively mobile, and thus it is easy to employ cross-fire, multiport, rotational, or more complicated techniques to improve the therapeutic ratio. With fixed machines. such as  $\pi^-$  and fast neutron sources, such techniques become more difficult. With a single fixed source and collimator, the single port and cross-fire techniques are relatively easy. Four-port techniques are feasible, but are undesirable and complicated. If a patient is rotated through 90° to obtain four-port exposure with a fixed source, the probability is high with most tumors that anatomic relationships will

have changed. This can be prevented, but only to a degree, by the cumbersome approach of body casts. With fixed sources it is highly desirable to have at least a horizontal and a vertical beam.

Damage to the skin is not a major limitation in most radiotherapeutic procedures, and thus relative skin sparing does not assume major importance in the comparison of different beams. The degree of skin sparing with  $\pi^-$  mesons has not been measured, but can be approximated. If the dose at several millimeters to 1 cm. in depth is taken as 100 units, the doses to the stratum germinativum are approximately:  $Co^{60}$  gamma rays, 30; 14 MeV neutrons, 60; 15 MeV electrons or  $\pi^-$  mesons, 90.

#### B. LET; CELL SENSITIVITY AND REPAIR

The selective advantages of the  $\pi^-$  beams in terms of absorbed dose pattern are considerably enhanced by virtue of the *selec*-

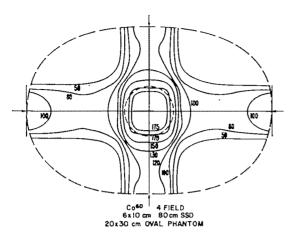


Fig. 7. Isodose curves, Co<sup>60</sup> gamma rays, 4 ports (Kligerman *et al.*, calculated.)

tive deposition of high LET radiation in the tumor, as opposed to low LET radiations in normal tissues unavoidably exposed. Advantages accrue in terms of: (1) relative increase in the absolute radiosensitivity (effect per unit dose) of the tumor as compared to normal tissue; and (2) a relative decrease in the ability of tumor cells to repair sublethal radiation damage.

The relative change in absolute radiosensitivity can be appreciated by comparing curve a and b in Figure 3. With conventional low LET radiations, dose-effect curves for both normal and tumor tissues lie in the plateau region of the  $\pi^-$  depthdose curve. However, tumor tissues selectively exposed to high LET radiation in the peak portion of the  $\pi^-$  beam will show a response between that of curves a and b, and probably much closer to a than to b. This change in absolute radiosensitivity, made possible by virtue of physical characteristics unique to the  $\pi^-$  beam, is reflected to a degree in the RBE discussed previously. For tentative planning purposes in evaluating the usefulness of negative  $\pi$  mesons in radiotherapy, RBE values for the peak portion of the  $\pi^-$  depth-dose curve of approximately 2 for single large exposures (compare curves a and b, Fig. 3), and 4 or more for fractionated large exposures or low dose rate application (compare curves a and c, Fig. 3) appear to be reasonable. Efforts to quantify further the degree of advantage from these values are given below.

#### C. LET; OXYGEN ENHANCEMENT RATIO

A further advantage in favor of normal tissues lies in the selectively lower OER in tumor versus normal tissue, by virtue of the high LET radiation confined essentially to tumor tissues. As indicated above, it appears reasonable for planning purposes to use an OER value of between 1.6 and 2.0 for the peak portion of the  $\pi^-$  depth-dose curve. Efforts to quantify the degree of gain from this are given below.

## D. "DOSE-EQUIVALENT" AND "EFFECTIVE DOSE" DEPTH CURVES

If high LET radiations are used, then one must consider, in addition to dose, the "dose-equivalent"\* or DE (absorbed dose in rads times RBE). Further, if one considers hypoxic cells in the tumor, then one must think in terms of the "effective dose" or ED, which is defined here as the DE  $\times 1/OER$ . In comparing the depth-dose characteristics of different radiations, the comparison must be made not only in terms

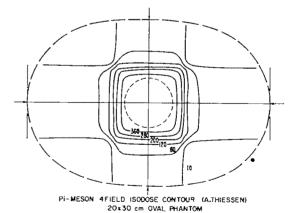


Fig. 8. "Isodose equivalent" curves,  $\pi^-$  mesons, 4 ports. The absorbed dose in the peak portion of the single axis curve is multiplied by an assumed RBE of 3.3 to obtain the "dose equivalent." (Kligerman et al., from Thiessen, calculated.\*2)

\*"RBE Dose," the older term for Dose Equivalent, is the quantity used to denote the product of absorbed dose and the quality factor. The term is limited in strict usage to Radiason Protection.

of dose, but in terms of dose equivalent and effective dose.

Schematic single-axis "depth-dose" curves for Co<sup>60</sup> gamma rays, 14 MeV neutrons, and π<sup>-</sup> mesons, showing absorbed dose, DE and ED are shown in Figures 9 to 11 (the tissue locations labeled T, A, A<sub>2</sub>, etc. are for use in Section IV, and are defined there). The shaded portion of the curves represents the "width" of the tumor in depth.

The curves are schematic because values of RBE and OER, necessary to calculate DE and ED, can for the most part be rough estimates only. Also, with respect to  $\pi^-$  mesons, the shape of the curves varies with the momentum spread of the beam. Thus exact comparisons are not possible and the curves presented must be regarded as illustrative only.

In Figure 9, for Co<sup>60</sup> gamma radiation, the solid line in the upper panel represents both absorbed dose and DE since the RBE is 1. In the lower panel, the ED for hypoxic cells is less than the DE by a factor of 1/3 (assumed OER of 3.0). In Figure 10 for fast neutrons, assumed values for RBE and OER are 3.0 and 1.5, respectively. Cor-

#### Co-60 GAMMA RAYS CENTRAL AXIS DEPTH DOSE

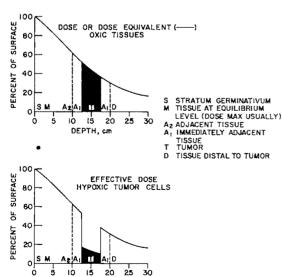
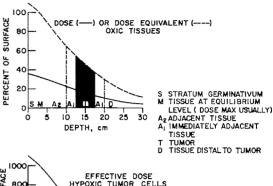


Fig. 9. Central axis depth-dose curves, Co<sup>50</sup> gamma • rays. Absorbed dose, dose equivalent, and effective dose (schematic).

#### 14 MeV NEUTRONS CENTRAL AXIS DEPTH DOSE



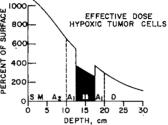
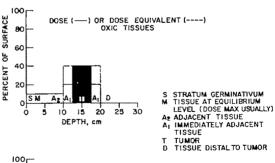


Fig. 10. Central axis depth-dose curves, fast neutrons. Absorbed dose, dose equivalent, and effective dose (schematic).

responding values assumed for  $\pi^-$  mesons (Fig. 11) are 2 and 1.5.

Although numerical comparison of relative dose equivalents and effective dose in

#### NEGATIVE PI MESONS CENTRAL AXIS DEPTH DOSE



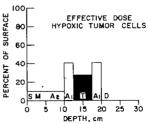


Fig. 11. Negative  $\pi$  mesons, central axis depth-dose. Absorbed dose, dose equivalent, and effective dose (schematic).

Figures 9 to 11 would not be valid, the curves are adequate to illustrate the fact that more than absorbed dose is required for precise intercomparison of the effectiveness of beams. Small differences in dose delivered to different cell populations could mean appreciable differences in cell survival rates, depending on absolute dose levels and the assumptions made with respect to the shapes of the dose-survival curves for the cell populations involved.

Although multiport dose equivalent depth curves are not shown, it can be seen easily that the ratio of dose equivalent tumor versus skin for  $\pi^-$  mesons might be 16:1 or greater with  $\pi^-$  mesons, as compared to perhaps 2 to 1 for Co<sup>60</sup> gamma rays. The corresponding ratios for effective dose might be 12 to 1, versus 2 to 1 or less.

## E. FRACTIONATION WITH THE $\pi^-$ VERSUS CONVENTIONAL BEAMS\*

Because the high LET component of the  $\pi^-$  beam is localized at the peak portion of depth-dose curve, and because of the differential in rates of recovery from sublethal cell damage, the advantages of fractionation versus single exposure with the  $\pi^$ beam would be expected to be much greater than those with conventional radiations or with fast neutrons. However, even excluding the high LET portion of the  $\pi^$ radiation, the  $\pi^-$  beam can deliver a higher dose of low LET radiation to the tumor than to normal tissue including that located near the tumor. Thus, even with single-port therapy, the therapeutic ratio for low LET radiation may be 1.5 to 1, and this might increase to 4 to 1 or greater with multiport therapy.

While the large therapeutic ratio obtainable with even the low LET portion of the  $\pi^-$  beam clearly is advantageous, it is less clear whether the added advantage with fractionation would be the same as (or predictable from) that obtained with conventional radiotherapy. The large tumor/normal tissue dose differential ob-

tainable with  $\pi^-$  mesons would appear to make it possible, in a single treatment session, to deliver a dose to tumor tissue that lies principally on the straight exponential portion of the dose-survival curve (Fig. 3, curve b), while delivering a dose to most normal tissue that lies well up on the "shoulder" region of the curve. The fractionation question cannot be answered with certainty, without sufficient, specific information, e.g., the precise shape of doseeffect curves for tumor and normal tissuejust prior to each treatment session, differential rates of cell repopulation, effects on stroma, etc., but a simplified version of the problem can be examined by assuming all biologic response factors, including doseeffect curves, to be identical for normal and tumor tissues. In what follows, the relative advantage of fractionation on identically responding normal and tumor cell populations is examined, when a favorable ratio of doses to the two populations are given.

Let the dose to tumor be r times that to normal tissue (with r>1), and let both cell populations be subjected to the same dose-survival curve, then one may write

$$ln S_N = f(D)$$
, and (1)

In 
$$S_T = g(D)$$
, where (2)

$$g(D) = f(rD)$$
, and (3)

where D is the dose to normal tissue.

If these curves have straight (exponential) portions with common extrapolation number, n, the equations representing them are

$$ln S_N = ln n - bD, and$$
 (4)

$$\ln S_T = \ln n - rbD, \tag{5}$$

where b is positive (Fig. 12).

We wish to examine the effect of fractionating the dose, assuming (a) full recovery between doses, and (b) a constant final survival fraction for normal tissue. Let this survival be designated  $S_N$ , and the total dose delivered in k fractions be  $D_k$ . So long as the single fraction, 1/k  $D_k$  gives points, each of which is on the straight portion of its curve, as indicated in Figure

<sup>\*</sup> The author is indebted to Dr. C. V. Robinson for invaluable aid in preparing this section of the report.

12, an increase of I in the number of fractions gives a decrement of  $(r-1) \ln n$  in the log survival of tumor. As soon as the point for normal tissue falls on the shoulder of its curve, the decrement is less. With further fractionation, tumor survival will, in general, reach a minimum value, which then corresponds to the optimum number of fractions. (Precise advantage depends on numbers.)

The conclusions are drawn that, with conventional radiotherapy, an added advantage accrues to normal versus tumor tissue with fractionation over a single exposure, when the dose per fraction to both normal and tumor tissue is high enough to be on the straight exponential portion of the curve and both cell populations are subject to the same dose-survival curves. The degree of added advantage, however, may be quite different with an actual  $\pi^$ beam, in which the dose per fraction to most normal tissues may be on the shoulder of the curve. The relative advantage could be greater or less, depending on the precise doses and fractionation pattern employed, and the values of the parameters that actually apply in the above equations.

These conclusions in no way indicate that fractionation with a  $\pi^-$  beam would not be advantageous over single-session therapy. The principal conclusion is that fractionation patterns known or assumed to be optimal with conventional therapy cannot be assumed to be optimal with  $\pi^-$  therapy, and that the most advantageous fractionation patterns with the new modality must be worked out, perhaps empirically, by actual use of the  $\pi^-$  beam.

# IV. ASSESSMENT OF THE IMPORTANCE OF SHARP DEPTH-DOSE PATTERNS

A glance at the single axis depth-dose curves for negative  $\pi$  mesons shown in Figures 5 and 6, compared with the single  $\pi$  axis depth-dose curves for more conventional radiations shown in Figure 7, serves to convince one that the  $\pi^-$  beam would be expected to be superior to more conventional radiations with respect to depth-

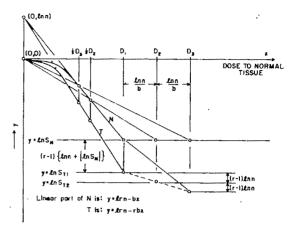


Fig. 12. Effect of fractionation of dose when normal tissue, N, and tumor, T, are subject to the same dose-survival curve, but receive doses in a constant favorable ratio r. The value of r illustrated is 1.25.

dose characteristics. The principal objective in radiotherapy, to improve the "therapeutic ratio," or the ratio of lethal tumor dose to normal tissue tolerance dose, obviously would be advanced with the  $\pi^-$  beam. The question, however, is how much better is the  $\pi^-$  beam?

How much better the  $\pi^-$  beam will be depends critically on the precise location of the normal tissue which becomes limiting in determining the amount of dose that can be delivered to the tumor. This can be seen most easily in the diagrammatic depthdose curves shown in Figures 9 to 11, in which tissues in different locations relative to the tumor are labeled. The tissue locations so labeled are defined as follows:

Tissue "T". The entire tumor to be irradiated.

Tissue "A<sub>1</sub>". The normal tissue immediately adjacent to, in, or invaginated into the tumor. This normal tissue will be irradiated to the same extent as is the tumor, no matter how well-tailored the beam may be.

Tissue "A<sub>2</sub>". Normal tissues adjacent to the tumor, in the "tumor bed," inevitably included in the radiation field with present radiation sources. Usually a dose gradient across these areas ex-

ists, varying in steepness with the therapy approach used.

Tissue "M". The layer of normal tissue located just below (mm. to cm.) the skin surface, where most conventional beams come to equilibrium and the dose to tissue usually is maximum.

Tissue "S". The stratum germinativum.

The skin sparing effect is usually thought of in terms of the dose to Tissue S versus that to Tissue M.

Tissue "D". "Distal" tissue, used to denote vital tissues in depth, beyond the tumor, which unavoidably will be heavily irradiated with most conventional beams if the proximal tumor is given a high dose.

If tissues S, M, or D were limiting, then the  $\pi^-$  beam would have a distinct and great advantage over conventional beams. If tissue  $A_2$  were limiting, the  $\pi^-$  beam would still be expected to have an advantage over conventional beams, although less distinct. If tissue  $A_1$  were limiting, then the  $\pi^-$  beam would have little or no advantage, in terms of depth dose, over conventional beams. (Compare particularly the relative effective doses to tissues A, and T, in Figures 9 and 10.)

That the  $\pi^-$  beam has greater advantage as the limiting normal tissue is further removed from the tumor is shown also in the multiport depth-dose curves in Figure 8. The dose to tissues close to the surface, relative to the tumor, can be greatly reduced by this technique. The closer these tissues are to the tumor, the more difficult it is to avoid high-dose exposure even with multiport techniques.

Few generalizations can or should be made with respect to the location of the limiting tissue with conventional beams, but some are in order. With modern techniques, the limiting tissue is rarely the skin (tissues S or M). In some specific cases, the limiting tissue is clearly D; e.g., the spine or kidney located "behind" a tumor. The degree to which tissues A<sub>2</sub> or A<sub>1</sub> may be limiting is more difficult to document. Ob-

viously, the thinner the layer of irradiated tissues in A<sub>2</sub> (the more closely the irradiated tissue in A<sub>1</sub>), the lower the expected morbidity and mortality rate. Also, there is no doubt that the smaller the total volume of normal tissue that is irradiated in treating a tumor (the sharper and more localized the beam is to the tumor), the better the therapeutic result.\* However, the degree to which sharply localized irradiation constitutes a clinical gain is very difficult to quantify, and few data are available. The reasons for this are several. To date the precise anatomic confines of a tumor generally have not been accurately known, and there have been no adequate methods available for localizing the deposition of energy to the confines of the tumor even if the anatomic confines were precisely defined. Also, most tumors are irregular in shape, and project irregularly into adjacent normal structures. For these reasons, it generally has been necessary to include normal tissues A<sub>1</sub> and A<sub>2</sub> in the beam, with the result that it is most difficult to say at present from clinical data which tissue is in fact limiting.

This problem has been examined<sup>31</sup> using the results of therapy in which the techniques currently in vogue at the University of Texas M. D. Anderson Hospital and Tumor Institute were employed. The approach was to estimate the probability of complications that result from radiation unavoidably administered to normal tissues inside and outside the "target volume," using photons in the 1–22 MeV/range. The "tumor volume" is defined as the high dose therapy region, and includes normal tissue suspected of having a high probability of micro-invasion by tumor, and which receives essentially the same high dose that

<sup>\*</sup> The concept that the smaller the volume of normal tissue included in the beam the smaller the morbidity and mortality rate, should be sharply differentiated from the concept that the degree of biologic effect depends on the total energy absorbed or the average dose (total gram-rads, gram-rads/gram). It has been shown clearly in a number of animal experiments that the degree of biologic damage depends primarily on the total dose in rads, the type of tissue included in the beam, and the over-all sensitivity of that tissue. Nonetheless, it will be clear intuitively that the smaller the amount of normal tissue of any type included in the beam the smaller will be the probability of complications.

is administered to the tumor (tissues A<sub>1</sub> and A<sub>2</sub>). The review of patients included those with tumor of the head and neck area (hypopharynx wall, pyriform sinus, oropharyngeal wall, and nasal pharynx), urinary bladder, uterine cervix, and bronchus. The results were evaluated in terms of the relative frequency of complications that arose in tissues outside the target volume versus the complications that arose within the target volume.

With respect to head and neck cancer (total of 448 patients), approximately 60 per cent experienced complications of one type or another. Approximately 10 per cent (41 patients) had complications only in tissues outside of the target volume. Another 37 per cent (165 patients) had complications only inside the target volume. Another 10 per cent (43 patients) had complications in both locations. Therefore, in a similar group of patients, one could expect that a more sharply localized beam would reduce the total proportion of patients with complications from a total of 60 per cent to approximately 50 per cent or less. In addition, another 10 per cent might have less severe reactions, e.g., complications only in the target volume.

In the bladder carcinoma group, a total of 2 per cent of patients had complications due to changes outside the target volume. In the carcinoma of the cervix group, only a very small percentage showed complications outside of the tumor area. For bronchogenic carcinomas, it was believed that a more sharply confined beam would facilitate palliation, but would not be expected to alter survival markedly. Similar results emerged with respect to treatment of carcinoma of the breast. More sharply localized irradiation was considered to offer significant advantages in the treatment of nasopharyngeal and esophageal tumors, and of the paraaortic region; e.g., metastases from carcinoma of the cervix, urinary bladder, or testes. From these data, it might be expected that a  $\pi^-$  beam would improve the over-all morbidity rate by some 15 per cent or less.

The studies described above re-emphasize the point that generalizations are essentially meaningless, and that each tumor type must be considered separately. No doubt estimates of the precise location of limiting normal tissues, and the reduction in morbidity and mortality to be expected if these tissues were avoided, could be improved with more extensive and largescale consideration of clinical results from several institutions. However, such additional surveys very likely would lead to basically the same conclusions, namely that the  $\pi^-$  meson beam would be advantageous over currently employed conventional beams, but the precise degree to which it would constitute an advantage could not be stated in the light of present knowledge.

The studies cited must not be considered as definitive in evaluating the possible advantages of a  $\pi^-$  beam. The beams employed were not as sharply confined as the  $\pi^-$  beam would be expected to be, and therefore, of course, the results do not represent a strict evaluation of the possibilities of that beam. Also, the target volume included tissues suspected of having a high probability of microscopic invasion by tumor. This volume might well be reduced were methods available to define better the confines of tumors (tissues presently considered to be in category A<sub>1</sub> might in fact turn out to be in category A<sub>2</sub>). This consideration highlights the fact that the borders of most tumors are not well known, and that relatively little experimental work has been devoted to improving methods of defining the tumor-normal tissue interface. It is apparent that better definitions of tumor boundaries would be necessary to utilize maximally the precise energy deposition possible with the  $\pi^$ beam.

It is important to consider the numbers of patients necessary to evaluate differences in results such as those discussed above, or in comparing the effectiveness of a  $\pi^-$  beam relative to more conventional approaches. If the improvement with a given type of

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lesion were the equivalent of 10 percentage points, a total of approximately 300-400 patients with that lesion would be required to detect this difference at p <0.05.

#### V. ASSESSMENT OF THE IMPORTANCE OF OER

In assessing the over-all importance of the possible advantages of  $\pi^-$  mesons with respect to OER, it is necessary to consider: (1) the availability of other sources of high LET radiations, adequate to test the hypothesis that anoxic cells now constitute a serious barrier to the control of tumors; (2) the availability of sources adequate for definitive high LET radiation therapy, if hypoxic cells are assumed or shown to be a serious limitation ameliorated by high LET sources; (3) the relationship of OER to dose-limiting normal tissue; and (4) the question of reoxygenation.

Fast neutrons represent the best currently available high LET source for these purposes. Measured values of OER have been approximately 1.6 or lower for neutron energies of the order of 14 MeV or less. The OER obtainable with such sources is in all probability at least as favorable as that obtainable in the peak region of the  $\pi^-$  meson depth-dose curve.

Beams of fast neutrons are currently being employed in England in radiotherapy, and it is probable that clinical tests utilizing implanted sources of fast neutrons (californium 252 needles) will start in the next several months in the United States. These approaches are considered adequate to evaluate the degree to which overcoming the problem of hypoxic cells will improve radiotherapy; however, it is probable that definitive answers will not be available for 5 years or more.

Machines capable of accelerating stripped high Z (Z of 8 or higher) particles to energies sufficiently great to achieve penetration of 10 or more cm. in tissue would be suitable and probably better than either fast neutron or  $\pi^-$  meson beams for testing the hypothesis, but the date when such a machine will be available is indefinite. Studies utilizing hyperbaric oxygen should

provide further input for evaluating the problem; however, definitive results have not become available as yet. Other approaches such as the use of hydrogen peroxide regionally, or the induction of hypoxia in normal and tumor tissue in the region of a tumor, such as is possible by interrupting the blood supply to a limb, should also contribute to evaluating the problem. Results to date are too sparse to provide definite answers.

On the basis of the above, there would appear to be inadequate justification for a high intensity beam of negative  $\pi$  mesons as a preferred agent in evaluating the importance of hypoxic tumor cells in radiotherapy.

Should it turn out that hypoxic tumor cells represent a significant limitation in radiotherapy that may be overcome in part by a high LET radiation, then the suitability of sources of high LET radiation for routine practical radiotherapy becomes a critical factor. In addition to a favorably low OER, the beam of high LET radiation must have suitable intensity and suitable depth-dose characteristics.

The most suitable high LET beam currently available is 14 MeV neutrons, which can be produced with an accelerator using the D, T reaction. Depth-dose curves for fast neutrons from this source compare favorably with those for Co<sup>80</sup> gamma rays; the output is not optimal at present. Considerable attention is being given to the possibility of developing sources, rotating collimators, and target cooling such that dose rates at the tumor would be more suitable for radiotherapy. Thus, to the degree that Co<sup>80</sup> gamma radiation can or should be used for radiotherapy, 14 MeV neutron beams may be used.

Since fast neutron beams are available that can be applied for practical use of high LET (low OER) radiations in radiotherapy, and since more suitable beams can be developed, it would appear difficult to justify a high intensity  $\pi^-$  beam on the sole basis that such a beam would be necessary to take advantage of the fact that high LET

 $Table \ \ II$  comparison of characteristics of co  $^{60}$  gamma, fast neutron and  $\pi^-$  meson beams

Co <sup>40</sup> Gamma Beam	Fast Neutron Beam	π Meson Beam		
Gradient of dose on tissue far from ideal, diminishing with depth	Gradient of dose on tissue far from ideal, diminishing with depth	"Neck area" less than 50 per cent of peak		
2. Not charged	Not charged	Charged, therefore can be deflected by magnets		
3. Relatively easy control of size and shape of entrance beam	More difficult control of beam size and shape; devices more bulky	Much finer control of beam size and shape by electromagnetic means		
4. Isodose contours controllable to a degree by collimation, wedging and diaphragm motion	Isodose contours much less easily con- trollable	Can be sharply controlled using mag- nets, collimation and computers		
5. Exit dose considerable	Exit dose considerable	"No" exit dose		
6. Large volume receives high dose in rela- tion to tumor-bearing volume	Large volume receives high dose in rela- tion to tumor-bearing volume	Volume receiving high dose can be tailored to the case		
7. Difficult or impossible to avoid sensitive organs	Difficult or impossible to avoid sensitive organs	Easier ("neck" of beam, no exit dose, less need of cross-fire)		
8. Maximum repair of cellular damage in tumor and normal tissues	Reduced repair in both tumor and normal	Cellular repair selectively reduced tumor		
9. Maximum OER in tumor and normal	Reduced OER in both tumor and normal	Selectively reduced OER in tumor only		
10. Adequate output	Adequate output (?)	Adequate output		
11. Skin sparing about 65 per cent	Skin sparing about 35 per cent	Skin sparing about 10 per cent		
12. Source can be rotated	Source cannot be rotated; only 4 ports available at present	Source cannot be rotated; only 4 ports available		

OER=Oxygen Enhancement Ratio.

radiation may ameliorate the problem of hypoxic tumor cells.

The importance of depth-dose and doselimiting normal tissues in relation to OER can be seen by comparing the "depth-dose" pattern in the lower panel of Figure 10 (fast neutrons) with that in the lower panel of Figure 11 (negative  $\pi$  mesons). Should the dose limiting normal tissue be S, M, A<sub>2</sub> or D, then negative  $\pi$  mesons pose a very significant advantage over fast neutrons with respect to the ratio of "effective dose" to hypoxic tumor cells, compared to that of the dose limiting normal tissue. However, should the dose limiting tissue be  $A_1$ , then negative  $\pi$  mesons have no advantage in this regard over a beam of fast neutrons. Also, in light of current knowledge, it probably would be most difficult to separate any advantages that may accrue from  $\pi^-$  meson therapy into that portion resulting from depth-dose and selective cell repair factor, and that due to a favorable OER. On this basis, the radiotherapeutic gain possible by use of high LET radiations would be better evaluated by use of fast neutrons, for which depthdose patterns are similar to those of conventional radiotherapy.

Finally, the importance of hypoxic cells in tumors, with respect to control of malignancy by means of radiotherapy, must be considered in the context of "reoxygenation" that is known to occur in some tumors between dose fractions of conventional low LET radiation. While the degree to which hypoxic cells represent a limiting factor in radiotherapy has not been established definitely, reoxygenation does not appear to eliminate the problem. It would appear that, if hypoxic cells are important in radiotherapy, a definite advantage would accrue by employing a beam of high LET radiation.

# Summary of characteristics of a $\pi^-$ beam of importance in radiotherapy

A comparison of the characteristics of  $Co^{60}$ , fast neutron, and  $\pi^-$  beams is given in Table II. The central axis depth-dose curve and the isodose contours of such a curve for negative  $\pi$  mesons can be readily manipulated to fit the individual tumor by altering the momentum spread and other

physical beam parameters by means of selective collimation, beam optics, or other means. This is by far the most important potential advantage of the beam. The peak region of the depth-dose curve can be spread out (and readily varied) to encompass tissue volumes of the order of 10 or more cm. in diameter. The dose throughout the peak region can be made to exceed that in the plateau region by a factor of the order of 2. With a beam of pure negative  $\pi$  mesons there is minimal lateral scatter, and essentially no exit dose. Thus the beam affords the best opportunity to date to "tailor" maximum dose contours to the actual outlines of the individual tumor.

# VI. AVAILABILITY OF $\pi^-$ AND OTHER BEAMS

No sources of  $\pi^-$  mesons for medical use, available now or definitely scheduled to become available, appear to be suitable for radiotherapy. The beams nearest to being available are in Zurich, Switzerland, and in Vancouver, Canada; however, expected outputs are less than optimal. Thus, if  $\pi^-$  mesons are to be used extensively and satisfactorily in radiotherapy, a source with higher intensity than any machine currently available or definitely scheduled for construction is required.

The Los Alamos Pi Meson Production Facility (LAMPF) currently under construction at Los Alamos Scientific Laboratory apparently would provide such a facility. The maximum dose rate delivered to a tumor would be approximately 100 rads/min. The beam would have negligible contamination from electrons or other undesirable radiations. Focusing and collimation to achieve shaping of the beam to "tailor" it to the individual tumor, such as is described in this report, is feasible.

Machines currently planned but not approved for construction in Berkeley would be capable of accelerating stripped nuclei of any Z to energies of 300 or more MeV per nucleon, with a resulting penetration of many cm. in tissue. The LET

of such beams is very high in both the plateau and peak regions, and the peak region probably can be widened, particularly with multiport therapy, to cover several centimeters. The depth-dose characteristics appear not to be as favorable as those of the  $\pi^-$  meson beam; however, the OER would be expected to be low, perhaps approaching unity. Such a beam obviously would have advantages in radiotherapy.

Beams of protons, alpha particles, deuterons, or tritons have been used successfully under some circumstances in which a 'pencil beam" is desired, e.g., pituitary irradiation. These beams offer fewer advantages in radiotherapy than does the  $\pi^-$  beam, because of their relatively narrow width compared to the dimension of most tumors, and because the LET of such beams, even in the major portion of the Bragg peak, is too low to provide a usable advantage with respect to OER. However, the Bragg peak can be "spread out" and an essentially flat depth-dose curve, or a curve with a peak portion of appreciable width, can be achieved.20 The rapid lateral fall-off obtainable with a wellcollimated  $\pi^-$  or e<sup>-</sup> beam is also obtainable with these currently available particles. Such beams to date have received only very limited use in radiotherapy, despite the fact that depth-dose patterns obtainable are appreciably better than those obtainable with currently used conventional beams. Available data are inadequate to assess their possible over-all advantage in the treatment of malignancy.\*

# SUMMARY

The negative  $\pi$  meson beam has a number of favorable characteristics which, taken collectively, make a high-output beam attractive for radiotherapy. These include: (I) a depth-dose and dose equivalent (dose  $\times$  RBE) pattern superior to those now available; (2) a relatively low OER in the peak portion of the depth-dose curve;

<sup>\*</sup>The author is indebted to the Atomic Energy Commission for permission to publish this modified version of the report of its Pion Review Committee.

and (3) less repair of sublethal cell damage in the peak portion.

The unique, and readily-tailored superior depth-dose patterns obtainable with negative  $\pi$  mesons would provide a distinct advantage in radiotherapy. The clinical gain to be expected from such sharply localized radiation is difficult to assess quantitatively from presently available data, and it is not possible to predict whether the over-all improvement in morbidity and mortality is likely to be 5 per cent, 10 per cent, or more.

The favorable OER is advantageous. This does not in itself constitute a compelling reason for making available a high intensity source of negative  $\pi$  mesons, since other currently available sources of high LET radiation, namely fast neutrons, are likely to be suitable for the evaluation of the importance of hypoxic tumor cells in radiotherapy and the degree to which high LET radiations may help to overcome this problem. The densely ionizing peak portion of the  $\pi^-$  meson depth-dose curve can be confined nearly selectively to the tumor volume. The resultant lower fraction of repairable damage in tumor versus most irradiated normal cells will result in favorable therapeutic ratios which become more favorable with lowered dose rate of fractionation.

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# BIOPHYSICAL ASPECTS OF HIGH LET IRRADIATION\*

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N ATTEMPTING to achieve maximum differences between the radiation effects on malignant and normal tissues, radiotherapists have utilized a variety of approaches. The simplest and most important of these is to attain an optimum dose ratio between tumor and normal tissues. Obviously this ratio should be as high as possible and, except for decisions on what normal tissues are unavoidably irradiated, no choices need be made. However, if differences in cell destruction are to be further enhanced by additional measures such as dose fractionation and administration of hyperbaric oxygen and other agents that modify radiation response, optimization is required, particularly if several of these methods are used simultaneously. Radiobiological research has, particularly during the last decade, greatly enhanced our understanding of the factors that might determine optimum conditions. These include dose-effect relations, recovery, division delay, change of age distribution of cells in the division cycle, oxygen enhancement ratio, revascularization of tissues and proliferation rate. Although many of these features are understood in some detail there is still not enough numerical information to permit practical applications and, consequently, the great majority of radiotherapy treatments are carried out following methods that have been in practice for decades.

A-major modification of radiotherapy is the employment of different radiations. The introduction of teletherapy gamma sources and high voltage accelerators for the production of very energetic x-rays or electrons has, in many cases, led to a substantial improvement in dose distributions but has hardly affected the role of other biophysical factors. At the highest energies

the biological effectiveness of these radiations might be decreased by perhaps 15 per cent, but there is much less, if any, change in differential sensitivities of tumors or in the action of dose modifying factors. All of these radiations have the common property of imparting energy to irradiated tissues through the agency of high speed electrons and they are sometimes termed low LET radiations. Their action differs in many respects from that of another group of radiations that are termed high LET radiations. These expressions are vague and, as will be shown, rather misleading. It is thus necessary to provide somewhat more definite dividing lines for the purpose of this discussion.

Linear Energy Transfer (LET) refers to the rate of energy loss of a charged particle traversing the medium of interest (in this case tissue). It is used to characterize radiation quality in the broadest meaning of this term. Unless subject to refinements LET cannot provide complete specification of radiation quality and even with these refinements it is usually found to be unsatisfactory in detailed theoretical considerations.4,5 However, the concept is simple and adequate for the discussion at hand. The LET of a charged particle depends on its velocity and on its charge. Electrons carry only one unit of charge and, as commonly employed in radiotherapy, spend most of their range at velocities that are between nearly 100 per cent and 20 per cent of the speed of light as the energy decreases from arbitrarily high values to about 10 keV. Once the energy has fallen below 10 keV the small mass of the electron causes it to be stopped within a few microns of tissue. Consequently, most of the electron energy is expended when the LET rises from its

<sup>\*</sup> Presented at the Fifty-second Annual Meeting of the American Radium Society, Coronado Island, San Diego, California, March 1-4, 1970.

Part of Symposium: High LET Radiation. Moderator, Michel Ter-Pogossian, Ph.D.
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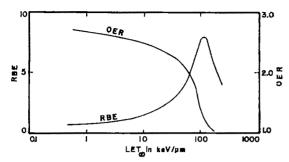


Fig. 1. Between 10 and 100 keV/µm, the OER (Oxygen Enhancement Ratio) decreases from near its maximum value to its minimum value of 1.0 and the RBE (Relative Biological Effectiveness) increases from a minimum characteristic for low LET radiations to a maximum near 100 keV/µm. The curve is for 1 per cent survival.

minimum possible value of about 0.2  $keV/\mu m$  to about 3  $keV/\mu m$ .\*

Nuclear particles have a much higher mass than do electrons. Hence for equal energies they have lower velocities and they maintain these low velocities for considerably longer portions of their track. In addition, nuclear fragments can carry more than I electronic charge. In order to have the 3 keV/ $\mu$ m LET of a 10 kilovolt electron, an alpha particle must have an energy of somewhat more than 70 MeV and a range of 3,500  $\mu$ m in tissue. Thus for the same LET the energy of the alpha particle is more than 7,000 times larger and the residual range more than 1,000 times larger. An alpha particle of 5 MeV has a range of about 40 microns, most of which is traversed at a LET in excess of 100 keV/um with a maximum around 175 keV/μm near the end of the range.

Roughly speaking, most of the changes in the biological action of charged particles occur in the decade between 10 and 100 keV/µm. This is illustrated in Figure 1 which is based on a presentation by Barendsen. It will be seen that between 10 and 100 keV/µm the OER (Oxygen Enhancement Ratio) decreases from near its maximum value to its minimum value of 1.0 and that the RBE (Relative Biological Effectiveness) increases from a minimum char-

acteristic for low LET radiations to a maximum near 100 keV/µm (the curve is for 1 per cent survival). The subsequent decrease of RBE is known to be due to constant cross section for inactivation, but the kinetics of "single hit" inactivation pertain at all LET values above 100 keV/µm. Todd6 has observed the same general behavior with a somewhat different course of the curves for the same kind of cells (T<sub>1</sub> kidney cells). The difference is, at least in part, probably due to limitations of the LET concept, but it is of little importance in these considerations. It would thus seem logical to classify radiations below 10 keV/µm as having low LET and above 100 keV/µm as having high LET and those in the interval as having intermediate LET. According to these categories, electron accelerators used in radiotherapy may well be termed sources of low LET radiation, but all of the so called "high LET" radiations that have been used, or currently could be used, for radiotherapy are principally of intermediate LET.

At present the only nuclei which are available at sufficient energy to penetrate several centimeters of tissue are hydrogen and helium. In order to have such penetration these nuclei must have energies of the order of 100 MeV and consequently LETs of the order of I keV/ $\mu$ m. Near the end of their range the LET of these particles increases, giving rise to the so-called Bragg peak of ionization. Although the attendant increase in absorbed dose makes such beams very useful for the production of small lesions at great depth in tissue, their value for radiotherapy is quite limited since all attempts to widen the zone of peak dose to more than I or 2 cm. have led to a rapid deterioration of the height of this peak. At any rate, only a small fraction of the peak dose in this region is due to particles of intermediate LET and even less due to high LET. In fact no protons of any energy ever quite reach the limit of high LET since the maximum LET of protons is about 95  $keV/\mu m$ . Since most of the absorbed dose of fast neutrons is delivered by recoil protons it follows that the accelerator sources

<sup>\*</sup> Consideration of secondary electrons (delta rays) requires modification of these statements. However, this is not necessary here and has been avoided for the sake of simplicity.

and californium sources which are or are about to be used in neutron radiotherapy are predominately sources of intermediate LET particles. Heavy recoiling nuclei produced by these neutrons may be considered to have high LET by the standards chosen here. However, the contribution of such particles becomes significant only if the neutron energy is so high that an appreciable fraction of the proton dose is delivered at low LET. Negative pi-mesons which, near the end of their range produce various nuclear disintegration products, have particularly attractive depth dose distribution that is characterized by a broad peak in which the LET of spallation products is higher than that of the mesons but generally somewhat lower than that of the neutron sources currently considered for radiotherapy.

The expression "generally somewhat lower" lacks precision and one should like to characterize the LET of these radiations numerically. However, attempts in this direction are confronted by considerable difficulties. In all instances the charged particles found at some point in the irradiated tissue have a wide range of LETs that can be completely characterized only by provision of a distribution which usually spans many decades. Attempts to define a meaningful average LET are seriously hampered by nonlinearity. Presumably one would define the average LET by the requirement that if all particles had the average LET, the effect observed would be the same as that produced by the actual distribution. With this definition the track average for 14 MeV neutrons is around 12  $keV/\mu m$ , the dose average somewhere between 80 and 90 keV/ $\mu$ m, the average for cell survival perhaps 25 keV/ $\mu$ m, and the average for oxygen enhancement ratio somewhere between 40 and 100 keV/ $\mu$ m, depending on whether Barendsen's or Todd's data are used. It should be mentioned that the averages for biological action are based on experiment. If one attempts to calculate them, substantially different values result, which indicates that it may be altogether impossible to predict the biological effects of a radiation on the basis of its LET distribution.<sup>2</sup>

It should be noted that most of these complications are due to the fact that these radiations are in the region of maximum change of radiobiological action. Radiobiology in the region of truly high LETs appears to be much simpler; indeed it is probably simpler than in the low LET range. However, as already pointed out, radiotherapy in this range is impossible with presently existing equipment. Provided other complications do not enter, one would expect high LET action throughout the range of nuclei having atomic numbers higher than about 20 and energies up to about I GeV. An accelerator capable of producing such radiations is at present under consideration but could not be available for radiotherapy for many years at

Currently available heavy ion accelerators have produced beams of such low energy as to be utterly unsuitable for radiotherapy. However, they have been employed in a considerable number of radiochemical and radiobiological studies on systems requiring only feeble penetration. This research has also included human cells in tissue culture. The results obtained with these and various other sources indicate that the principal differences between low and high LET radiation are those given in Table 1. The properties of the radiations which are the subject of this symposium generally fall between these extreme characteristics.

Table I may be summarized by stating that the injury produced by a single low LET particle is comparatively moderate, in that by itself it is usually insufficient to kill the cell and is also subject to modification by a variety of circumstances; on the other hand, a single high LET particle traversing the cell nucleus is generally lethal regardless of circumstances. When these conditions are met, it is a simple matter to calculate  $D_0$  (the dose required for 37 per cent inactivation) for any cell having a spherical nucleus. If L is the LET in keV/ $\mu$ m, and d the nuclear diameter in

Table I

Action of high and low let radiation on mammalian cells in tissue culture

	Low LET (<10 keV/μm)	High LET $(> 1\infty \text{ keV}/\mu\text{m})$
Cell survival curve	Sigmoid	Exponential
Sublethal damage	Present	Absent
Recovery*	Present	Absent
Biological effectiveness	Low with little dependence of LET	High but decreasing with increasing LET
Change of sensitivity during cell division cycle	Pronounced	Minor
Effect of dose modifiers	Appreciable	Negligible
OER	2.5-3.0	~I
Dependence of radiosensitivity on cell type	Considerable and probably complex	Minor and probably proportional to nuclear diameter

<sup>\*</sup> This term applies to intracellular recovery of the Elkind type and not to tissue repair processes. OER=Oxygen Enhancement Ratio.

microns, then

$$D_0 = 20L/d^2$$
 rads.

It would appear that this relation is at least approximately correct above LET values in excess of  $2\infty$  or  $3\infty$  keV/ $\mu$ m. For cells other than those normally employed in *in vitro* studies, these remarks might have to be modified with respect to low LET but hardly with respect to high LET.

At first sight the crude and nonselective action of high LET radiation would seem to be a serious detriment in radiotherapy where fractionation and other methods are employed to obtain optimum differential effects between malignant and normal cells. Although it is well established that some tumor cells can be very poorly oxygenated, it is still not clear whether this factor is important in fractionated treatments in which there might be a continuous transfer of cells from the anoxic to the oxygenated compartment. However, even if anoxia were an important factor, the employment of high LET radiation would merely render the sensitivity of malignant cells equal to that of normal cells except for differences in nuclear size.

These considerations leave one with the impression that it is perhaps fortunate that what are termed "high LET radiations" are in fact radiations of intermediate LET, leaving at least the possibility that one

might find a set of irradiation conditions (e.g., fractionation schedules) which result in improvements over conventional radiotherapy. In view of the complexity of the factors involved, attempts to establish such conditions on a theoretical basis are difficult and uncertain, and empirical approaches will be of paramount importance. It must therefore be hoped that radiotherapists exploring the potentialities of "high LET" radiation will be flexible as well as enthusiastic.

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# EFFECTS OF FAST NEUTRONS ON HUMAN SKIN\*

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A FAST neutron beam was first used for radiotherapy in 1938,18-20 only a few years after discovery of the particle. Between 1938 and 1943, Stone 18 and Stone and Larkin<sup>19</sup>treated 24 patients with the 37 inch cyclotron and 226 with the 60 inch apparatus at Berkeley. The disease in most of these patients was advanced and only 18 survived 5 years or longer after the neutron therapy. Although many early skin reactions were severe, Stone and Larkin<sup>19</sup> concluded that the late damage was greater than expected on the basis of early reactions. Because of the discouraging conclusions drawn by Stone,18 radiotherapy with fast neutrons was abandoned for nearly 20 years.

Renewed interest in fast neutrons for cancer therapy derived from the observation that the Oxygen Enhancement Ratio (OER) for neutrons is less than for roentgen rays.14 In contrast to roentgen rays, fast neutrons should inflict relatively more damage on hypoxic tumor cells than on well-oxygenated normal tissues. Many other factors, of course, may influence the clinical effectiveness of fast neutrons relative to roentgen rays.8 Experiments at the Hammersmith Hospital in London on the skin of pigs indicated that the Relative Biological Effectiveness (RBE)\* of fast neutrons increases with decreasing size of dose.6 Fowler and Morgan<sup>12</sup> suggested that the early workers were unaware of this phenomenon and, consequently, may have overdosed many of their patients. The RBE for late damage of pig skin was, reportedly, no different from that for early damage after either a single dose or fractionated exposures.<sup>5</sup> These results were confirmed in studies of the rat skin. 10,11 Once a critical level was reached in these rats, a slightly increased dose changed the early reaction minimally, but increased the late damage greatly. The relationship between early and late damage, however, was the same for roentgen rays and fast neutrons in both single and fractionated doses. Much more information is now available on the interpretation of various schemes of dose fractionation and on the physical characteristics of absorbed neutron energy. In view of these facts, we have re-evaluated the observations of Stone and Larkin<sup>19</sup> relative to the effects of neutrons on human skin. Fortunately, their records are still available and most of them are fairly detailed. Many include color photographs of the skin reactions.

# METHOD

The records of the 250 patients given neutron therapy in Berkeley between September 1938 and February 1943 were reviewed in detail. Particular emphasis was placed on the results in the 17 patients from which Stone drew his conclusions for the 1947 Janeway Lecture. 18 Only a few patients were treated on the 37 inch cyclotron and these received relatively small and usually single treatments. Therefore these patients (1 of whom had survived 5 years) were not considered further.

The site and extent of tumor in each of the 226 patients treated on the 60 inch machine were tabulated. The condition of

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<sup>\*</sup> RBE is defined as the ratio of the dose of roentgen rays to that of neutrons to produce an equal biological response.

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TABLE I

GRADING SYSTEM FOR SKIN EFFECTS FROM NEUTRONS FROM BERKELEY 60 INCH CYCLOTRON

Early reaction (	0	to	2	months	after	therapy	)
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Grade o-no change evident

Grade 1-slight erythema

Grade 2—marked erythema, heavy pigmentation or dry desquamation

Grade 3-moist desquamation

3-A-involving less than total treatment area

3-B-involving total treatment area

Grade 4—ulceration which failed to heal within 2 months after completion of therapy

# Late reaction (2 or more years after therapy)

Grade o-normal appearing skin

Grade 1—change in pigmentation, epilation

Grade 2—slight to moderate telangiectasia, atrophy, fibrosis

Grade 3—marked telangiectasia, atrophy, fibrosis

Grade 4-ulceration, necrosis

the skin before therapy was specified. Radiation other than neutrons, size, and location of treatment field, and number of individual treatments were noted. The individual dose and the total dose (in n units) and the over-all treatment time were also tabulated. From the descriptions and the color photographs, all early and late reactions of the skin were graded (Table 1). Early reactions were judged on the basis of observations during the first 2 months after neutron therapy. The late reaction was judged according to the changes noted 2 years or more after the end of therapy. Probably some late reactions would have been greater, had the patients lived longer. Of the 226 patients treated on the 60 inch cyclotron, only 25 were observed longer than 2 years (Table II) and only 17 for 5 years or more. In some patients with severe reactions during treatment, radiotherapy was interrupted while the skin healed. Such interruption undoubtedly reduced the severity of the early reaction, but its influence on the late reaction is difficult to evaluate. These patients, when identifiable, were eliminated from the study. It should be noted, however, that because of technical problems with the cyclotron, many patients received treatments at irregular intervals. Four patients are still living and have been examined by the present authors within the past year.

The 60 inch cyclotron at Berkeley produced neutrons by bombarding beryllium with deuterons having an energy of approximately 16 MeV. The design of the apparatus, beam monitoring, and the beam collimation were similar to that for the 37 inch cyclotron, which has been described in detail. The beam monitor was calibrated against a 100 R Victoreen chamber and the readings recorded as n units. The output of the apparatus was about 5 n of neutrons per minute, equivalent to about 12 rads per minute at the treatment distance of 100 cm.

# FACTORS IN ESTIMATING THE EFFECTIVE ABSORBED DOSE

Depth dose. The neutron beam produced by the Hammersmith cyclotron is similar to that of the 60 inch Berkeley cyclotron and the data on depth dose obtained on the 2 machines agree well.<sup>7,17</sup> In the present study the more extensive depth dose data from

Table II

PATIENTS TREATED BY NEUTRONS AT
BERKELEY, 1938 TO 1943

Therapy with 37 inch cyclotron	•	24
a. Record lost	I	
Therapy with 60 inch cyclotron		
1. Discarded from present study		82
a. Previous irradiation	44	
b. Concurrent roentgen therapy	2	
c. Roentgen therapy immediately		
after neutrons	50	
d. Interrupted neutron therapy 1		
month or more	4	
e. No observation recorded	4 26	
f. Record lost	I	
2. Included in present study		144
a. Reaction observed for only 1 year		
or less	106	
b. Reaction observed for >1 but		
<2 years	13	
c. Reaction observed for 2 or more	-	
years	25	
Total	-	20

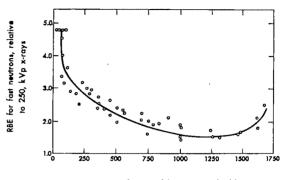
Hammersmith have been used, with a correction for source-skin distance, to calculate exit doses. Exit doses were not considered by Stone and Larkin.<sup>19</sup> Where fields are opposed and allowed to extend to the edge of curved surfaces, e.g., bilateral neck fields which include the anterior surface, the exit dose approaches 100 per cent. This situation, of course, is accompanied with loss of whatever skin-sparing may occur with fast neutrons.

Build-up. Several studies have shown that with fast neutrons absorbed energy builds up in tissue, with a maximum reached at about 1 mm. below the surface.<sup>3,18,16</sup> Such build-up might be expected to reduce the apparent early skin reaction. This reduction would not necessarily influence the late reaction if the late reaction results from damage to deeper tissues.

Recent data obtained at the Hammersmith Hospital by placing tissue-equivalent plastic of I mm. thickness over one-half of the exposed area of human skin indicated that with this neutron beam some skinsparing does occur, but that the effect is probably insufficient for clinical importance.<sup>3,4</sup> In addition, loss of sparing of the skin of Stone's patients may have resulted from placement of the patient directly against the collimator opening. For these reasons, corrections for build-up and skinsparing were not attempted.

Backscatter. Measurements by Bewley and Parnell<sup>7</sup> indicated that for correction of backscatter of radiation within tissue, the air doses given by Stone should be increased by 6 to 8 per cent for treatment fields of 10×10 cm. to 10×15 cm. The 7×7 cm. test-fields used for estimation of RBE and for conversion of the n unit to rads should be corrected similarly. Since these two corrections are relatively slight and tend to be similar, no correction for backscatter has been made.

Increased absorption in fat. Since fat has a higher hydrogen content than other soft tissues and the effectiveness of neutron absorption is related to the hydrogen concentration, fatty tissues absorb more energy



Dose per fraction of fast neutrons (rads)

Fig. 1. RBE (Relative Biological Effectiveness) for fast neutrons relative to 250 kVp roentgen rays, plotted against size of individual neutron dose. Data from studies of Stanley B. Field at Hammersmith Hospital.

than other tissues from a neutron beam. When the fat is thick enough to give equilibrium conditions and the dimensions of blood vessels are less than the range of the secondary radiations, the dose in such vessels increases 15 to 20 per cent. Increased absorption in fat may explain the greater reaction in fields of the buttocks as compared with other sites for a given calculated dose. No numerical correction for this absorption in fat could be made.

For a precise estimate of the absorbed dose, and hence, full interpretation of the skin damage reported by Stone and Larkin, 19 certain factors should be considered. These include exit dose, build-up, backscatter, and increased absorption in fat. We were able to correct, however, only for exit dose.

Conversion of n units to rads of neutrons. Stone's records show that a single dose of 110 n of fast neutrons from the 60 inch machine produced a threshold of erythema. With 250 kVp roentgen rays, the threshold erythema dose is 730 rads (extrapolated from Johns<sup>16</sup>). Field's data<sup>11</sup> (Fig. 1) related RBE for neutrons to the size of the dose. Based on these data, 730 rads of 250 kVp roentgen rays are equivalent to 265 rads of fast neutrons (i.e., with this dose the RBE is 2.8). Thus, 110 n units appear to be equivalent to 265 rads so that 1 n would be equivalent to 2.4 rads of fast neutrons. This

factor is in excellent agreement with the factor of 2.5 in terms of roentgens as Aebersold and Anslow<sup>2</sup> suggested on physical grounds.

Calculation of skin dose. For each fraction of radiation exposure, the recorded dose in n units was multiplied by 2.4 to convert it to rads of neutrons. It was then multiplied by the RBE factor for 250 kVp roentgen rays selected from Figure 1, and divided by 0.85 to convert to an equivalent dose of megavoltage roentgen rays. The last step was introduced to facilitate comparison with current radiotherapy experience. The individual doses were summed up to produce a total, equivalent, entrance dose of megavoltage roentgen rays in rads. Exit doses (with few exceptions opposed fields were treated on the same day) were calculated and added to the entrance dose.

The neutron treatment regimens used by Stone and Larkin<sup>19</sup> included a wide range of total dose, over-all treatment time, and number of dose fractions. To compare the effects of their neutron treatments with effects produced by conventional radiation therapy, the equivalent megavoltage roentgen-ray dose in rads was next converted to the nominal single dose (NSD). For this purpose we used the formula developed by Ellis: Total dose =  $NSD \times N^{0.24} \times T^{0.11}$ , where N is the number of fractions and T is the over-all treatment time. Since in this formula 0.24 is the factor that allows for recovery between individual fractions of roentgen-ray exposures, the formula is strictly valid only for roentgen rays. We believe, however, that since allowance was made for the variation of RBE with size of each dose fraction, this formula can be applied to neutron exposure after conversion to equivalent doses of megavoltage roentgen rays.\*

The Ellis formula and tables are probably not valid for doses given in fewer than 4 fractions. Therefore, when the treatment consisted of only 2 or 3 fractions the calculations were modified. The NSD for 2 fractions was calculated on the assumption that recovery after I fraction is equivalent to 500 rads of roentgen rays.11 Thus the NSD for a dose given in 2 fractions is the total minus 500 rads equivalent of megavoltage roentgen rays. For a 3 fraction treatment, the value for the NSD was obtained by interpolating between the results achieved with this 2 dose method and that obtained by our application of the Ellis formula for 4 doses. Although Ellis expressed the belief that the NSD would probably not produce precisely the same effect as an actual single dose, we had no alternative but to accept that dose as the NSD when a patient received only I treatment. Finally, the NSD was converted to the equivalent of a dose delivered in 30 fractions over a period of 6 weeks (SWD) according to the formula: SWD = NSD/0.293.

Although the effects of fractionation differ for neutrons and roentgen rays, we believe that the method used provides the best basis available at the present time for comparison of patients treated by such diverse dose-fraction schemes. The results of these calculations allow a comparison between the effects on the skin of neutrons and of megavoltage roentgen rays (when bolus is used) on the basis of both NSD and SWD. Because of the modifications introduced into the NSD calculations, we have chosen to express the results in rads rather than in rets (rads equivalent therapeutic) as was done by Ellis.

# RESULTS AND DISCUSSION

The effect of neutron exposure on the skin and subcutaneous tissues could be judged in 275 individual treatment fields in 144 of the 226 patients treated on the 60

<sup>\*</sup> To check the validity of this procedure, it was compared to an alternative method offered by Bewley. Based on an analysis of his data for the effects of neutrons on pig skin, Bewley suggested that a factor of  $N^{0.08}$  would fit the neutron results and that a proper formula for the conversion of total neutron rads to an NSD might be: Total dose=NSD $\times N^{0.08}\times T^{0.11}$ . The resultant NSD would be in terms of neutron rads which could be converted to megavoltage roentgen-ray rads by use of the appropriate RBE

factor. The NSD values for the Stone and Larkin neutron patients surviving more than 1 year were calculated by both methods and the results agree with each other by  $\pm 5$  per cent.

Table III

EARLY REACTIONS—DOSE VERSUS TREATMENT TIME

Grade No. of Fields	No. of	NSD	Over-all Treatment Time (days)				
	NSD	Individual	Average				
4	6	<2,8∞	13, 15, 26, 31, 31, 35	25			
4	8	$>2,8\infty$	15, 29, 32, 33, 33, 33, 34	30			
3	5	<1,6∞	2, 3, 15, 21, 31	14			
3	13	$>2,6\infty$	13, 13, 26, 30, 33, 33, 38, 38, 50, 53, 57, 57, 71	39			
2	13	<1,4∞	1, 1, 1, 1, 1, 1, 3, 3, 15, 15, 21, 24	7			
2	9	$>2,2\infty$	18, 36, 36, 40, 40, 57, 57, 58, 58	44			
I	3	<1,4∞	I, I, I	I			
I	4	$>2,\infty$	41, 45, 59, 59	51			

NSD= Nominal Single Dose.

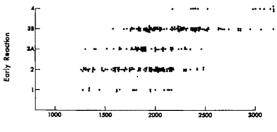
inch cyclotron. In the other 82 patients the effect could not be determined. In some of these, either no suitable observation had been recorded or the course of neutron therapy had been interrupted. In others the effect of the neutrons could not be distinguished from those of other radiation exposure.

Early reactions. The grade of the early skin reaction for each of the 275 treatment fields is plotted as a scatter diagram against the NSD in Figure 2. Although grade of reaction and NSD were directly related (shown better in Figure 3), the range of doses yielding each grade of reaction is broad. This spread probably resulted partially from lack of precision in retrospective grading of skin reactions and in part from biologic variability. The method of calculating NSD may also be a factor.

To determine whether some of the spread may have resulted from the method of calculation, the fields represented at either end of the dose scale of each early reaction grade were examined in detail (Table III). This Table indicates that a given grade of reaction is more likely to be associated with a low NSD if over-all treatment time is short. Conversely, a particular grade of reaction was associated with a high NSD when the course of treatment was extended. For example, a Grade 2 reaction resulted from nominal single doses of from 1,260 to 2,480 rads. In Grade 2, however, the treat-

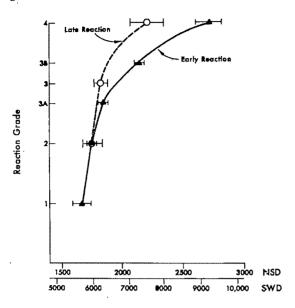
ment time averaged only 7 days when the NSD was less than 1,400, whereas it averaged 44 days when the NSD exceeded 2,200 rads. In general, short treatment times were associated with a small number of dose fractions and longer treatment times with more fractions. Thus, the NSD calculations may not fully compensate for the widely varying numbers of fractions and time intervals used in these patients.

Table IV shows the number of fields in which each specific grade of early reaction developed in each range of NSD. These data show that: (a) some visible reaction developed in every treated field; (b) early reactions were of Grade 3 or 4 in 60 per cent; (c) the NSD in more than 50 per cent was 2,000 rads or greater; and (d) although a wide range of doses was represented in each reaction grade, in general the higher the NSD the greater the likelihood of a more severe reaction.



NSD, Equivalent rads of megavoltage X-rays

Fig. 2. Grade of early skin reaction plotted against the NSD (Nominal Single Dose) in rads for 275 neutron treatment fields.



Equivalent rads of megavoltage X-rays

Fig. 3. Grade of early and late reactions for all treatment fields that could be evaluated plotted against both NSD and SWD (Six Week Dose) in rads. Ranges shown are the standard error of the mean.

To compare these neutron exposures to clinical experience, the early reactions were also related to the nominal SWD. Nearly 80

Table IV

EARLY REACTION FROM VARIOUS

NOMINAL SINGLE DOSES

NSD	N	Total Fields				
•	0	1	2	3	4	- Pieds
<1,200						0
1,200 to 1,399		3	12	1		16
1,400 to 1,599		I	9	3		13
1,600 to 1,799		5	20	16		4I
1,800 to 1,999		4	18	40		62
2,000 to 2,199		4	24	34	1	63
2,200 to 2,399			5	27	2	34
2,400 to 2,599			4	18	3	25
2,600 to 2,799				6	0	6
2,800 to 2,999				5	1	6
3,000 to 3,200				2	7	9
70 . ICII						~
Total fields	0	17	92	152	14	<b>2</b> 75
Per cent		6	34	55	5	

NSD= Nominal Single Dose.

Table V

LATE REACTION FROM VARIOUS

NOMINAL SINGLE DOSES

NSD	Nu	Total - Fields				
	0	I	2	3	4	- Picids
1,200	)					0
1,200 to 1,399	)			1		I
1,400 to 1,599	)			2		2
1,600 to 1,799	)		4	5	I	10
1,800 to 1,999	)			11	4	15
2,000 to 2,199	)	•	I	9	5	15
2,200 to 2,399	)			3		3
2,400 to 2,599	)				2	2
2,600 to 2,799	)					0
2,800 to 2,999	)					0
3,000 to 3,200	)				3	3
	-					
Total fields	0	0	5	31	15	5 I

NSD=Nominal Single Dose.

per cent of the fields had received 6,000 rads or more SWD and values in more than 50 per cent were ≥7,000. Of the 14 Grade 4 early reactions, 12 had received 8,000 or more SWD. Furthermore, 91 per cent of fields in which epidermolysis developed had received at least 6,000 rads SWD. Our experience with 1 MeV roentgen ray and Co<sup>60</sup> radiation therapy given with bolus, although difficult to quantitate, suggests that the neutron-induced early skin reactions were consistent with the doses applied.

Late reactions. Evaluation of both early  $(\leq 2 \text{ months})$  and late  $(\geq 2 \text{ years})$  reactions was possible for I treatment fields in 25 patients. The relationships between NSD, treatment time, and severity of late reactions are shown in Tables v and vi. As with the early reactions, the greater the dose the higher the grade of late reaction (Table v). With a NSD of fewer than 2,000 rads, the reactions were graded 4 in 5 of 28 fields. When the NSD was between 2,000 and 2,400 rads, 5 of 18 reactions were Grade 4 as were all 5 given 2,400 rads or more. Although in the Grade 4 late reactions a lesser dose appeared to be associated with a shorter over-all treatment time, too few

Grade No. of		NSD	Over-all Treatment Time (days)				
Fields	Nan	Individual Patients	Average				
4	5	<2,∞∞	29, 29, 8, 15, 15	19			
4	10	$\geq_2,\infty$	38, 60, 58, 29, 8, 32, 53, 34, 48, 48	41			
3	19	<2,000	23, 29, 29, 27, 45, 46, 47, 15, 24, 54, 15, 15, 8, 45, 25, 25, 25, 17, 17	28			
3	12	$\geq$ 2, $\infty$	26, 54, 15, 41, 29, 22, 8, 34, 30, 8, 24, 22	26			

NSD = Nominal Single Dose.

late reactions were observed to permit an adequate evaluation of the influence of treatment time on late reaction grade (Table vi).

Comparison of early and late reactions. Of the 31 fields with late marked atrophy or fibrosis, 26 had epidermolysis during or immediately after therapy (Table VII). In 13 of the 15 fields with late ulceration, epidermolysis had developed early and in 3 cases it had not healed 2 months after conclusion of therapy. Among the 10 patients (15 fields) with late ulcerative reactions, 5 had carcinoma of the prostate, 2 of the lip, 1 of the vocal cord, and I of the buccal mucosa, and I had a fibrosarcoma of the shoulder. All 7 fields in which a late Grade 3 or 4 reaction developed, but which had shown only a Grade 2 early reaction were in patients with carcinoma of the prostate. The 2 fields with early Grade 2 and late Grade 4 reactions had the most protracted therapy, namely 58 and 60 days, of those in the entire group observed 2 years or longer. In 4 of the 5 patients with prostatic carcinoma, ulceration occurred in the fields over each buttock. These patients with prostatic carcinoma received a NSD of 1,800 to 2,100 and a SWD of 6,1∞ to 7,150. Of the 5 with late ulceration and malignancy other than in the prostate, 4 had received a NSD of 2,520 to 3,220 (8,600 to 11,000 SWD) and the other had received a NSD of 1,910 (6,520 SWD). These observations tend to support the concept that when thick layers of fat underlie the skin, ulceration occurs at

lower doses than elsewhere in the body.

In Figure 3, the mean NSD is plotted against reaction grade for both early and late reactions. The ranges are shown as standard error of the mean. The severity of the late reaction tends to parallel that of the early reaction, but rises more rapidly relative to dose. This result may be an artifact arising from the grading schemes used in early and late reactions. In rat skin exposed to roentgen rays or neutrons, the late reaction tends to increase rapidly once a certain threshold level is reached.<sup>10</sup>

If a Grade 2, or at most, a Grade 3-A is accepted as the maximum permissible early reaction, and a Grade 3 is the maximum permissible late reaction, the maximum tolerable NSD from Stone's neutron irradiations is about 1,800 (Fig. 3) in terms of equivalent rads of megavoltage roentgen rays. This NSD is in accord with current experience (Ellis, 1968) and adds confidence to the mathematical procedures employed in this analysis.

Other observations. In addition to the 25 patients observed for more than 2 years after treatment, 9 (16 fields) were observed for 1 to 2 years. Although in these the late reactions were still progressing, a similarity in degree of severity of the early and late reactions was already evident. An early epidermolysis had covered the entire treated area of the 6 fields in which ulceration developed 1 to 2 years after neutron exposure.

That the Grade 3 or 4 early reactions did represent severe reactions is borne out by

Table VII

EARLY REACTION VERSUS LATE REACTION; NUMBER
OF FIELDS OBSERVED 2 OR MORE YEARS

Grade of		Grade	of Late	Reaction	ns	Total – Fields
Early – Reac- tion	0	I	2	3	4	- Fields
0						0
1						0
2			1	5	2	8
3			4	26	10	40
4					3	3
				*******		
Total fields	0	0	5	31	15	51

the associated complications. Early reactions in 12 patients were graded 4 (Table VIII). Of these 12 patients, 3 died within 2 years from hemorrhage or edema and respiratory obstruction secondary to radiation necrosis. In 4, who died of cancer within 2 years after treatment, radiation-induced ulcerations were still unhealed at the time of death. Of the 4 patients of this group who survived 2 years, all required full-thickness skin grafts or amputation, or both, of the irradiated part. Eventually these grafts sloughed. Moreover, 5 patients with Grade 3-B early reactions died as a result of: local radionecrosis, 2; pulmonary fibrosis, 1; bowel perforation, I; or cervical myelitis, I.

The Janeway Lecture of 1947. In the Janeway Lecture of 1947, 18 17 patients who were followed 5 years or more were considered in detail. Observations in these patients strongly influenced Stone's ultimate conclusions. Because of previous radiation therapy to the area included in the neutron field, 4 of the 17 have been excluded from the present study. Tumor site, field size, NSD, SWD, early reaction, and late reaction for the remaining 13 patients are presented in Table 1x. Excluding Patient 5, who had no severe late reaction, the SWD for this group of patients ranged from 6,400 to 11,000 rads. An early epidermolysis had developed in all of these treatment fields. The minimum SWD to produce late marked fibrosis and atrophy without ulceration was 6,400 rads (NSD 1,870). The minimum for late ulceration was 6,520 rads SWD (NSD 1,910). Of the 9 fields in which late ulceration developed, all had had epidermolysis or ulceration that failed to heal at the time of treatment. In retrospect, the roentgen-ray equivalent doses and the early reactions in these 13 patients were consistent with the delayed cutaneous and subcutaneous damage.

Patients 8 through 12 of Table 1x deserve additional comment. In each, a carcinoma of the prostate was treated via 2 10×15 cm. gluteal fields and a 10×10 cm. anterior field placed at the base of the penis. All 3 fields were directed toward the prostate. With this arrangement the anterior field received radiation from the exit beams of the posterior fields. In some cases this exit contribution was largely offset by a lower given dose to the anterior field. With NSD of 1,870 to 2,010 (SWD 6,400 to 6,900), late reactions of Grade 3 or 4 occurred in all 15 fields. In only 1 other patient (Patient 2) did such a reaction develop with NSD of less than 2,100. Perhaps, as suggested by Bewley,8 areas that include a large content of fat are more sensitive to neutron irradiation. On the other hand, this observation may be an artifact since of all patients treated to areas other than the prostate, only 1 (Patient 2) was a long-term survivor whose NSD was less than 2,100.

Cancer control by neutrons. The clinical material of this study was composed of a

Table VIII •
12 patients with grade 4 early reaction

Patients surviving fewer than 2 years		8
Died of cancer, reaction unhealed	4	
Died of cancer, reaction healed	I	
Died due to radiation necrosis	3	
Patients surviving 2 or more years		4
Required skin grafts over sacrum	I	•
Mandibulectomy and skin grafts	I	
Amputation	I	
Tracheostomy, skin grafts	I	•

TABLE IX "JANEWAY LECTURE" PATIENTS WITHOUT PREVIOUS RADIATION TO THE SAME FIELD

Patient	Tumor Site	Field Size	NSI	CHIP	Reaction Grade		
ratient	t attent 1 timor Site	(cm.)		SWD -	Early	Late	
I	Vocal cord	7× 7	2,520*	8,600*	3, 3	4, 4	
2	Neck lymph nodes	7×10	1,910	6,520	3	4	
3	Neck lymph nodes	7× 7	2,350	8,050	3	3	
4	Parotid	8×10	2,360	8,040	3	3	
5	Parotid	10×10	1,780	6,060	3	2	
6	Parotid	5× 7	2,160	7,370	3	3	
7	Skin	10×10	2,260	7,700	3	3	
8	Prostate	10×15	2,010	6,9∞	3, 3, 3†	3, 3, 3†	
9	Prostate	10×15	2,010	$6,9\infty$	3, 3, 3†	3, 4, 4†	
10	Prostate	10×15	1,880	6,450	3, 3, 3†	3, 3, 3†	
11	Prostate	10×15	1,965	6,700	3, 3, 3†	4, 4, 4†	
12	Prostate	10×15	1,870	6,400	3, 3, 3†	3, 3, 3†	
13	Shoulder	10×10	3,220	11,000	4	4	

<sup>\*</sup> Opposed fields overlapping anteriorly. Dose at overlap considerably higher.

† Anterior pelvic field, 10% to cm. (directed toward base of penis). NSD=Nominal Single Dose; SWD=Six Week Dose.

broad spectrum of malignant neoplasms. In general, the descriptions of the diseases were not sufficiently detailed to permit retrospective staging. Because of the advanced disease in most of these patients, no form of radiation therapy could have been expected to be curative. Furthermore, in many patients the neutron beam did not include all of the cancer. Thus, no conclusions regarding the relative efficacy of neutrons and roentgen rays in the cure of cancer can be drawn.

# .SUMMARY AND CONCLUSIONS

The observations on patients treated with neutrons from the 60 inch Berkeley cyclotron between 1938 and 1943 are reviewed and reinterpreted. This investigation is concerned only with the effects of neutrons on skin and subcutaneous tissues.

Utilizing data that relate the relative biological effectiveness (RBE) for neutrons to the size of the dose-fraction, the neutron doses were converted to equivalent megavoltage roentgen doses. When applicable,

factors were introduced to account for the contribution from exit beams. The timedose-fractionation pattern varied from patient to patient and usually was inconsistent with schemes used in current radiation therapy. Therefore, the doses were calculated in terms of a nominal single dose (NSD) and a nominal 6 week dose (SWD). The NSD and SWD allow some comparison with conventional radiation therapy.

Suitable for inclusion were 144 patients with 275 separate fields treated with the 60 inch cyclotron. Among this group were 25 survivors, with 51 treatment fields, who were observed 2 years or more after neutron therapy was completed. Early reactions were judged according to findings during the first 2 months after treatment. The late reactions were graded according to observations 2 or more years after therapy.

The data indicate that: (a) the roentgenray equivalent of the neutron doses applied was relatively large in comparison with conventional megavoltage roentgen-ray therapy; (b) an early reaction was visible in all treatment fields and in 60 per cent this amounted to epidermolysis; (c) the late reactions were severe in most patients who survived 2 years or longer, but in 80 per cent of the fields epidermolysis had developed at the time of treatment; (d) fields in which late ulceration developed had received SWDs of 6,100 to 11,000 (mean  $7.800 \pm 500$  rads); (e) tissues with a high content of fat appeared to have a greater reaction; (f) the "calculated" tolerance SWD for this neutron trial is about 6,100 rads; and (g) after the tolerance dose is exceeded, the severity of the late reaction appears to increase more rapidly as a function of dose than does the severity of the early reaction, but this may be related to the grading schemes used.

With the proper allowance for exit dose, fractionation scheme, and change of RBE with fraction size, both early and late skin reactions can be accounted for on the basis of dose received. Furthermore, the late reactions seem generally consistent with the early reactions. Lack of knowledge regarding (a) the influence of the fractionation scheme on tissue response, (b) possible skin-sparing with fast neutrons, and (c), as suggested by the Hammersmith group, the change of RBE with fraction size may have caused the earlier workers to underestimate doses applied and to misinterpret the significance of the early skin reactions. We believe that the Berkeley neutron data from 1938 to 1943 should not contraindicate a properly planned and controlled clinical investigation of neutron therapy.

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# CLOTTING FACTORS AND METASTASIS FORMATION\*

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THE surgeon is seldom at a loss to explain his failure to control primary tumor growth if a critical, unbiased evaluation is made of: (a) the gross findings at surgery; (b) whether a truly encompassing en bloc resection of the tumor was carried out; (c) the gross and/or microscopic adequacy of the surgical margins, as sometimes determined by step-section slide preparation; and (d) the cellular characteristics of the tumor.

The failure to control metastases is less easily explained in view of the surgeon's:
(a) "gentle manipulation" of the tumor;
(b) early ligation of all draining vessels and lymphatics; (c) chemical or radiologic attempts to preoperatively decrease the viability of tumor cells that might have been dislodged from the primary tumor mass at the time of surgical manipulation; and (d) assurance that preopertively all radiologic, isotopic and physical findings failed to reveal any evidence of tumor dissemination.

The many unknowns surrounding the dilemma of "metastases" along with the poorly understood road blocks which face the experimental transplantation immunologist, have directed the investigative interests of many experimental laboratories into the field of tumor immunology. It appears very likely that many of the previously unexplained and bizarre behavior patterns of tumor cells may find some meaningful explanations through a better understanding of the immunologic mechanisms associated with the tumor-host relationship. However, just as important and more easily understood by the nonimmunologically oriented clinician or investigator is the growing body of knowledge calling attention to the importance of blood coagulation phenomena that may be associated with metastases or, more specifically, to the role that precipitation of fibrin and its deposition may play in the development of metastatic foci of growth.

#### MECHANISMS OF METASTASES

While the basic mechanisms of metastases are poorly understood and the explanations often are only theoretic,15 it is generally agreed that certain fundamental steps can be outlined, based upon rather extensive experimental understanding.87 The cancer cell enters the blood and/or the lymphatic circulatory system by active invasion or passive intravasation. As has been demonstrated by the cytologic identification of tumor cells in the circulating blood and lymph, 1,2,84, the cells are systemically disseminated, with the blood or lymph serving as the vehicle.44 Fortunately, most of the cells are destroyed as they pass through the circulating system. That certain cells reach the stage of lodgment and growth is indicated by the subsequent development of metastases. Apparently, the cancer cell must first adhere to the capillary endothelium where it becomes entrapped or enmeshed by a network of fibrin and platelets. The resultant microthrombus obliterates the exacting and discrete definition of the usual capillary endothelium. Normal circulating cells then migrate through the capillary wall which no longer serves as an efficient barrier to the individual cells.39 The larger tumor cells may then be attracted through this inefficient endothelial barrier and find entrance to the extravascu-

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lar spaces. A fibrin stromal precipitate serves as a tumor bed allowing vascularization, growth and multiplication of the tumor cell. 40,42,43 Obviously, this is a very over-simplified explanation of the metastatic processes, but only limited understanding is available to fully describe such a complex mechanism. 38 However, it is within these fibrin-dependent steps of entrapment and stromatization that is found the most obvious site for the interaction of the blood coagulation mechanisms.

# EXPERIMENTAL ANTICOAGULATION

The identification of tumor thrombi or emboli in various states of thrombin formation and degeneration has long been recognized and used to account for both the cause of, as well as the prevention of metastases. It is only in the past decade, however, that many of the theories of several well established investigators11,12,27,81,82,88,85 have been clarified by the experimental studies of Cliffton, 6,8,10 Agostino, 3,4 Lacour et al.,16 and Wood.86 O'Meara identified, at the invading periphery of several experimental tumors, a lattice-like formation of thrombin deposition which was interpreted as promoting tumor growth. 19,20 This fibrin formation appeared to be induced by what he called a cancer-coagulation factor, later called thromboplastin by Thornes et al.29,80 Both in the experimental rabbit tumor and in the human, Thornes and his associates were able to block the action of this coagulative factor by using anticoagulants. The repetitive demonstration that tumors in several experimental systems could be reduced in size with controlled anticoagulative measures further encouraged Wood and co-workers41 to demonstrate the same tumor dispersing action on the metastatic potential of a cancer. They noted that an enveloping microthrombus about embolic tumor cells was decisive in the mechanism of endothelial adherence and penetration.

While Retick and associates<sup>22</sup> in this laboratory found the effect of heparinization on the primary tumor not at all en-

couraging, their work did serve as a stimulus for continued interest in the anticoagulative mechanisms involved with tumor growth as well as metastases. Subsequently, through the initiative of Orme and Ketcham, 21 Ryan and co-workers 28,24,25,26 and Sugarbaker,28 we have been able to successfully establish an anticoagulation regime for small animals which allows anticoagulation at a prothrombin time level of 2 to 3 times over normal. Animals are able to undergo surgery without significant mortality or morbidity. With the added assistance of individual housing of animals, thus eliminating the colony-housing problems of fighting, competing for food and cannibalization of tumors of the weak animals, a series of experimental studies have emphasized the role that anticoagulation may play in decreasing the instance of metastases in tumor-bearing animals.

## METHOD

Anticoagulation was obtained by placing sodium warfarin (coumadin) in the drinking water of animals who were individuallyhoused throughout all the studies. The dosage was regulated with frequent prothrombin times utilizing Miale and Winningham's<sup>17</sup> micromethod and periorbital venous blood. When a stabilized level of anticoagulation had been reached of 2 to 3 times normal prothrombin time, all animals were given subcutaneous leg inoculations of tumor suspension prepared by the cytosieve technique, using third generation methylcholanthrene induced fibrosarcoma which originated, and has since been transplanted in C57/BL/6N mice. A nonanticoagulated control group of animals was concurrently injected with tumor. Twenty animals from each of the treated and control groups were killed weekly, with a recording of their prothrombin times, primary tumor weight and the incidence of pulmonary metastases (Table 1).

Using the anaplastic sarcoma T241 of Lewis in C57/BL/6N mice and the mammary adenocarcinoma in C<sub>3</sub>/HeN mice, both of which had been carried in our

TABLE I THE COUMADIN DOSAGE, PROTHROMBIN TIMES AND EXPERIMENTAL RESULTS OF THE ANTICOAGULANT EFFECT UPON THE NUMBERS OF TUMOR METASTASES AND THE SIZE OF THE PRIMARY TUMORS USING A THIRD GENERATION METHYLCHOLANTHRENE-INDUCED FIBROSARCOMA IN C57/BL/6N MICE

		Week	Following T	umor Inocu	ılation	
	I	2	3	4	5	6
Dose of coumadin (mg./1,000 cc. drinking water)						
Control	0	0	0	0	0	0
Coumadin	9.1	9.4	9.4	9.1	9.4	9.4
Prothrombin times Control (sec.)						
Coumadin	9.5	9.3	10	9.3	8.4	9.1
1. No. animals > 1 min.	7	ó	0	13	0	2
2. Average of remaining animals	,			3		
(sec.)	40	18	24	40	10	21
Number of mice with pulmonary metastases*						
Control	0/20	6/20	10/20	10/20	13/20	16/21
Coumadin	0/20	1/20	3/20	5/20	4/20	5/21
Average number of pulmonary metastases†						
Control	0	1.8	3.1	4.0	5.2	3.9
Coumadin	0	2	1.7	3.6	1.5	1.2
Average weight of primary tumor (gm.)‡						
Control	0.16	0.4	4.0	5.3	9.6	13.8
Coumadin	0.16	0.4	i.6	3.5	5.6	8.2

<sup>\*</sup> Over-all difference, p<0.001, Wilcoxon test for doubly censored data.

laboratory through many transplant generations, similar studies were performed using identical standardized experimental conditions. Again, tumor was injected into the deep subcutaneous tissue of the leg in both coumadin-treated and untreated animals and pulmonary metastatic comparisons made at 5 interval times during the next 3 weeks (Tables II and III).

# RESULTS

In all 3 experimental tumor host systems there was consistently a significant decrease in the instance of and numbers of pulmonary metastases in anticoagulated animals as compared to the control, nonamputated groups. In these systems, deaths with pulmonary metastatic disease were 1 less frequent as among those animals not anticoagulated. In addition, the primary tumor growth rate and the primary tumor mass in treated animals were always less than in the noncoagulated subjects. A review of Tables 1, 11 and 111 clearly demonstrates these highly significant differences and justifies the enthusiasm with which we have undertaken subsequent studies. For instance, in Table 1, at the 6 weekly intervals following tumor inoculation there were 2 to 6 times more metastases found in the lungs of noncoagulated animals. At the 3rd through the 6th week of study the average number of pulmonary metastases was I to 4 times greater at each interval. At the 3 to

<sup>†</sup> Over-all difference, p<0.05, Wilcoxon-Mann-Whitney rank order. ‡ Difference, p<0.01, for 4 to 6 weeks, Wilcoxon-Mann-Whitney rank order.

5 week follow-up period, the average weight of primary tumors was I to 3 times greater in the control animals who had no anticoagulation. Results are even more dramatic with the Lewis T24I sarcoma where 73 per cent of the control animals developed metastases as compared to 15 per cent of those treated with coumadin. For each metastatic lesion found in the coumadin-treated C57 mice, there were 12 lesions in the untreated controls. In the C1H mice, 6 lesions were found among the controls for each one identified in the treated animals.

In this and subsequent experiments the favorable correlation between the finding of fewer metastases with anticoagulation has been observed even when tumor-bearing animals have had their primary tumor removed by amputation. In these yet incomplete experiments, half of the animals which were anticoagulated previous to tumor inoculation were continued on coumadin through surgery and for a period of time postamputation.

# DISCUSSION

Wood et al.<sup>41</sup> have reported that the failure of development of an endothelial adhering microthrombus about embolic tumor cells resulted in a failure of cells to adhere to and then penetrate the endothelium and, therefore, did not reach the fibrinrich extravascular spaces. The fate of these cells which were subsequently dislodged

Table II

PULMONARY METASTATIC SPREAD FROM LEWIS T241
IN COUMADIN TREATED AND UNTREATED

C57/BL/6N MICE

Groups	No. of Mice	No. with Metas- tases	Total No. of Metas- tases	Metas- tases/ Mouse with Metas- tases*
Control	100	73	365	5.0
Coumadin treated	100	15	29	2.0

<sup>\*</sup> Difference significant, p<0.02, / test.

Table III

PULMONARY METASTATIC SPREAD FROM MAMMARY
ADENOCARCINOMA IN COUMADIN TREATED
AND UNTREATED C<sub>2</sub>H/H<sub>c</sub>N mice

Groups	No. of Mice	No. with Metas- tases*	Total No. of Metas- tases	Metas- tases/ Mouse with Metas- tases
Control	100	62	236	3.8
Coumadin treated	100	15	41	2.7

<sup>\*</sup> Difference significant, p<0.01-99 per cent confidence interval computation.

into the general circulation has not been identified. It is apparent that anticoagulation may interfere with the formation of tumor microthrombi with the result that metastatic foci of tumor, particularly pulmonary in location, occur at an incidence which is significantly below that found in animals deprived of coumadin anticoagulation. While agents inducing a hypercoagulable state may increase the incidence of metastases, <sup>5,9,10</sup> pilot studies indicate that coumadin may completely reverse this hypercoagulant status.

The fact that primary tumor weight and size are reduced in anticoagulated mice is not completely explained. Cellular activity and metabolism have been shown to be affected by warfarin and it may be that primary tumor growth retardation is a result of this direct cellular effect, rather than through the anticoagulative action which may reduce fibrin formation.29 Possibly, the actual decrease in the primary tumor growth is accountable for the reduced incidence of metastatic spread, but it appears that while the explanation of depressed primary growth and metastatic spread might be similar, they can act independently one from the other. This was demonstrated by the anticoagulant and fibrolytic activity of numerous agents which were noted to decrease the metastatic spread following direct tail-vein tumor inoculation.7,9,18,14

Among patients receiving anticoagulant

therapy for a variety of thromboembolic diseases, Michaels18 reported a significant decrease in the metastatic spread of tumors developing in this patient population. The incidence of cancer was unchanged, but both survival and frequency of metastases were statistically better than would have been predicted. Now that refined laboratory methods are available for accurately and carefully monitoring the anticoagulant level of blood and in view of the experimental and clinical data available on anticoagulation and its relation to tumor spread, it appears that clinical studies should be considered. It is proposed that a tumor such as the human sarcoma, which often develops pulmonary metastases and only too frequently demonstrates the full metastatic potential to which malignant disease is capable, might make for an appropriate group of patients to study. Preliminary plans are now underway, at this Institute, to initiate a clinical program to investigate the role that anticoagulation may play in controlling metastases in surgical patients with localized resectable sarcoma.

#### SUMMARY

Nearly all experimental data available implicate the role of anticoagulation in the mechanism of metastases. Using 3 separate experimental tumor-host systems in mice, the growth rate of an implanted, primary tumor can be significantly reduced with sodium warfarin induced anticoagulation. In all experimental test conditions a surgically safe prothrombin time prolongation of 2 to 3 times normal increased the longterm survival, cure rate and evidence of metastatic tumor dissemination in all experimental models. While complications from bleeding were occasionally encountered, surgery could be performed safely and anticoagulation levels satisfactorily monitored and stabilized.

There is good experimental documentation to warrant a proposed clinical adjuvant anticoagulation study to determine if coumadin may effect a reduction in metastatic spread and subsequent cure-rate in patients who are to undergo surgery "for cure" of localized malignant disease, particularly the sarcomas which have such tremendous propensity for hematogeneous metastasis.

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# THE ROLE OF THE REGIONAL LYMPH NODES IN THE DEVELOPMENT OF HOST IMMUNOLOGICAL RESPONSE TO TUMORS\*

By YOSEF H. PILCH, M.D., DAVID S. BARD, M.D., and KENNETH P. RAMMING, M.D. BETHESDA, MARYLAND

IN 1964, Richmond Prehn stated: "Regional lymph nodes should be preserved whenever possible unless grossly tumorous. Radical dissections to remove all nodes should not be performed, but repeated surgery to remove nodes as they become grossly tumorous is probably preferable."19 This conclusion was admitted by the author to be speculative and based on the theoretic assumption that to remove the regional lymph nodes draining a tumor would most probably be detrimental to the host's immunologic response to that tumor. Three years later, in 1967, George Crile, Jr. quoted Prehn's statement and added. ... surgeons should realize that prophylactic excision or radiation of the regional nodes that drain small tumors not only increases morbidity but in some types or stages of cancer, may increase the death rate from distant metastases."7 He based this conclusion, at least in large part, on studies performed in his laboratory using 3 transplantable murine tumors which had been serially transplanted numerous times in his and other laboratories for many years.7,8 One must remember, however, that Prehn himself pointed out elsewhere in the same paper quoted above that, "Tumors that early in their natural histories are highly immunizing may lose this capacity in whole or in part during subsequent transplant generations."19 This phenomenon has been documented by several investigators, 18,20,25 and such tumors are now generally considered to be unsuitable for rigorous studies in tumor immunology.

During the 1950s, Mitchison<sup>17,18</sup> demon-

strated that cells from the regional lymph nodes of mice bearing allogeneic tumors could adoptively transfer immunity to these tumors within mice of an inbred strain but since these tumors were allografts, the immunity studied was due largely to histocompatibility antigens rather than to tumor specific transplantation antigens. The tumors were used instead of skin grafts as test grafts for the study of transplantation immunity. Recently, Delorme and Alexander have demonstrated the adoptive transfer of immunity to benz(a)pyreneinduced sarcomas in inbred rats with syngeneic, allogeneic and xenogeneic immune thoracic duct lymphocytes<sup>9</sup> and with lymphocytes obtained by cannulating the efferent lymphatic of regional lymph nodes in sheep which had been immunized with an implant of rat tumor.2 Studies performed more recently in our laboratory have shown the adoptive transfer of tumor specific transplantation immunity by regional lymph node cells within a completely syngeneic tumor-host system.6 There seems little doubt then that regional lymph node cells from appropriately immunized animals will adoptively transfer immunity to tumor specific transplantation antigens. But then, so will lymphocytes from other lymphoid organs of specifically immunized animals; i.e., the spleen.

In order to derive data to support or refute the hypothesis that removal of the regional lymph nodes draining a tumor adversely affects the host's immunologic response to that tumor, an animal model was devised to provide answers to the fol-

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TABLE I
EXPERIMENTAL DESIGN

	Right Regional Lymphadenectomy	Right Sham Lymph- adenectomy	Right Hind Limb Amputation	Side of Tumor- cell Challenge
Tumor-bearing mice				
Group 1	+		+	+ (left)
Group 2	+			+ (left)
Group 3	+			+ (left)
Group 4		+	+	+ (left)
Group 5		+		+ (left)
Group 6		+		+ (left)
Group 7 (unoperated controls)	1			+ (left)
Normal mice				
Group 8	+			+ (right)
Group 9		+		+ (right)
Group 10	+			+ (left)
Group II		+		+ (left)
Group 14 (challenge controls)		·		+ (right)

lowing basic questions: What is the function of the regional lymph nodes in the host's response to a primary tumor cell inoculum? What is the function of the host's regional lymphoid tissues during the growth of a tumor? What is the function of the regional lymph nodes after a tumor has been excised and the host re-inoculated with cells from the same tumor?

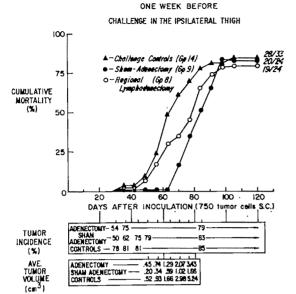
# MATERIAL AND METHOD

The tumor used in these studies was a fibrosarcoma induced by 20-methylcholanthrene in a female C<sub>1</sub>H/HeN mouse. It was used in its second and third transplant generations. One hundred and ninety-eight female C1H/HeN mice were inoculated above the right knee with 108 viable tumor cells. When tumors reached 6-10 mm. in diameter, 56 mice underwent a right regional lymphadenectomy, 29 mice underwent a right regional lymphadenectomy followed immediately by amputation of the tumor-bearing limb, 55 mice underwent a right sham lymphadenectomy, and 30 mice underwent a right sham lymphadenectomy combined with amputation of the tumor-bearing limb. Twenty-eight tumorbearing mice served as unoperated con-

trols. At the same time, 79 normal mice underwent right regional lymphadenectomy and 80 normal mice were subjected to sham lymphadenectomy. This experimental protocol is summarized in Table 1. One week later each mouse was challenged with 750 viable tumor cells. The tumor cells were injected into the left thigh in those animals which had undergone amputation of the right leg and in those animals with a growing tumor in the right thigh. Two groups of tumor-bearing mice, one having undergone regional lymphadenectomy, the other having undergone sham lymphadenectomy, were not challenged (Table 1). At weekly intervals, tumors were measured with a vernier caliper in two right-angle diameters, and the mean diameter was used to calculate individual tumor volumes assuming spherical growth. The tumor incidence, rate of tumor growth, and animal mortality were plotted for all groups.

## RESULTS

In normal mice (Fig. 1) in which a regional lymphadenectomy or sham lymphadenectomy had been performed I week prior to tumor challenge in the ipsilateral



REGIONAL LYMPHADENECTOMY OR SHAM ADENECTOMY

Fig. 1. The effect of prior regional lymphadenectomy on the growth of a primary chemically induced tumor when 750 tumor cells were inoculated into the ipsilateral thigh distal to the lymphadenectomy. Gp=group.

SHAM ADENECTOMY

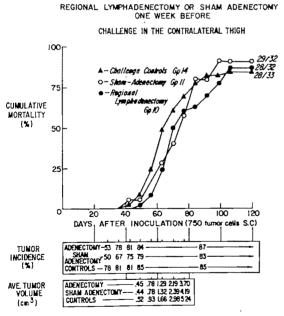


Fig. 2. The effect of prior regional lymphadenectomy on the growth of a primary chemically induced tumor transplant when 750 tumor cells were inoculated into the contralateral thigh. Gp=group.

MORTALITY OF MICE WITH GROWING THIGH TUMORS REGIONAL LYMPHADENECTOMY, SHAM ADENECTOMY, OR NO OPERATION

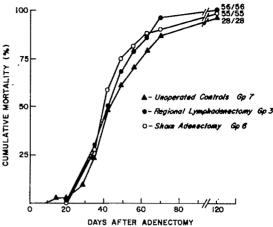


Fig. 3. The effect of regional lymphadenectomy on the growth of an established chemically induced tumor transplant. Gp=group.

thigh, the tumor incidence and final cumulative mortality in the 2 groups were essentially the same as in the unoperated challenge controls.

In those groups of normal mice (Fig. 2) undergoing a unilateral regional lymphadenectomy or sham lymphadenectomy 1 week prior to tumor inoculation in the contralateral thigh, there was no significant difference in cumulative mortality, tumor incidence, or mean tumor volumes between these 2 groups and the unoperated challenge controls.

As is shown in Figure 3, the cumulative mortality of mice with an actively growing thigh tumor was virtually the same whether the animals had undergone a regional lymphadenectomy, sham lymphadenectomy, or no operative procedure.

In those animals having undergone regional lymphadenectomy or sham lymphadenectomy combined with amputation of the tumor-bearing limb, there was no growth of the tumor cell challenge in either group, as is shown in Figure 4. Both experimental groups evidenced equally strong immunologic responses to challenge inocula of tumor cells.

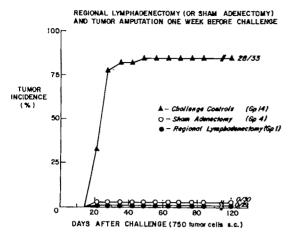


Fig. 4. The effect of regional lymphadenectomy on the resistance of mice in which the tumor-bearing limb was amputated to a subsequent challenge with the same chemically induced tumor. Lymphadenectomies and amputations were performed at the same time. Gp=group.

Of incidental interest was the finding (Fig. 5) that, when mice in which tumorbearing limbs had not been amputated (Groups 2 and 5) were challenged in the opposite thigh with cells from the same tumor, no growth of this second inoculum occurred. The host resistance to challenge inocula in these groups of mice was essentially the same as in those animals (Groups I and 4) from which the tumor-bearing limb had previously been amputated.

#### DISCUSSION

FUNCTION OF THE REGIONAL LYMPHOID TISSUES IN THE HOST'S RESISTANCE TO A PRIMARY TUMOR TRANSPLANT

The role of the regional lymph nodes in the host's resistance to a primary tumor cell inoculum was studied in 2 experiments (Fig. 1 and 2). It was expected that, if the regional lymphatics and lymph nodes played a major role in host resistance to a primary chemically induced tumor transplant, a decreased resistance to tumor growth would be observed following extensive regional lymphadenectomy because the afferent arc of the immune response (antigen processing) had been interrupted and regional immunocompetent tissue had

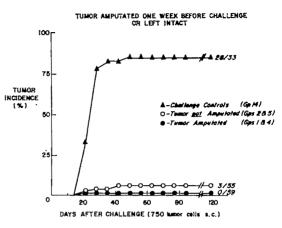


Fig. 5. Incidence of tumor takes following challenge of tumor-bearing mice and mice having undergone amputation of the tumor-bearing limb. Gp(s) = group(s).

been removed. This was not found in the present study. In fact, there was virtually no difference in mean tumor volumes, tumor incidence, or mortality among the groups. No evidence was found to support the hypothesis that removal of the regional lymphatics and lymph nodes in any way interferes with the host's response to a primary tumor transplant.

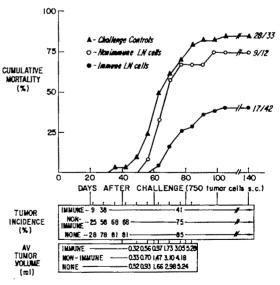


Fig. 6. The adoptive transfer of immunity to a chemically induced tumor by 10<sup>8</sup> regional lymph node cells obtained from donor mice in which transplants of the same tumor had been allowed to grow. LN=lymph node.

FUNCTION OF THE REGIONAL LYMPHOID
TISSUES IN THE HOST'S RESISTANCE TO
AN ACTIVELY GROWING TUMOR
TRANSPLANT

In mice with an actively proliferating tumor transplant (6–10 mm. diameter), excision of the regional lymphatics and lymph nodes had no effect on subsequent growth of the tumor or on host mortality when compared with those mice subjected to sham lymphadenectomy or with the unoperated controls (Fig. 3). This suggests that once a tumor transplant is established, removal of the regional lymph nodes has no significant effect on the host's ability to resist further growth of the tumor.

FUNCTION OF THE REGIONAL LYMPHOID TISSUES
IN AN IMMUNIZED HOST'S RESPONSE TO
SUBSEQUENT CHALLENGE WITH
THE SAME TUMOR

Animals subjected to amputation of the tumor-bearing limb, but no other procedure, were highly resistant to subsequent challenge with the same tumor, indicating that previous contact with the tumor had induced immunity in these animals. When the regional lymphatics and lymph noces were excised at the time of amputation of the tumor-bearing limb, all animals remained equally resistant to tumor cell challenge (Fig. 4). Even when the tumorbearing limb was not amputated at the time of lymphadenectomy or sham lymphadenectomy, virtually all animals continued to be resistant to the challenge tumor inoculum (Fig. 5). The observation that animals bearing growing tumors may exhibit resistance to subsequent transplants of the same tumor has been referred to as concomitant immunity.

In a previous communication from our laboratory, we reported that removal of the spleen significantly reduced the immunized host's resistance to subsequent inoculation with cells from the same tumor. Our present experiments, however, have failed to demonstrate a comparable decrease in the immunized host's resistance to tumor challenge following removal of regional lymph nodes. It may be that, while splenec-

tomy causes a significant depletion of the host's total population of immunocompetent cells, removal of the regional lymphatic tissues does not impair the organism's ability to respond normally to an antigenic stimulus. Moreover, if the regional lymph nodes are an important site of antigen processing, their role in mediating the immune response must have been completed prior to the time of lymphadenectomy. It is also possible that the regional lymph nodes play an important role in the initiation of an immune response to antigenic tumors under normal conditions but that, upon removal of the local lymph nodes, other more proximal lymph nodes assume their functional role.

It is important to stress that regional lymphadenectomy did not in any way adversely affect an immune host's resistance to a subsequent challenge with cells from the same chemically induced tumor, nor did it affect the growth rate of an actively growing tumor transplant. No evidence was obtained from these studies to support the contention that regional lymph node dissection may adversely affect host resistance to cancer.

Further experiments were then designed to study the role of the regional lymph nodes as well as the spleen in the initiation of the immune response; i.e., antigen pro cessing. Alexander and his group had observed an antitumor action with RNA extracted from specifically immune lymphocytes obtained from the thoracic ducts of rats suitably immunized with benz(a) pyrene-induced rat sarcomas and withRNA extracted from lymphocytes obtained from the regional lymph nodes of sheep immunized with the same rat tumor.1,8 These RNA preparations inhibited the growth of isografts of the same benz(a)pyrene-induced rat sarcoma used to immunize the RNA donor but had no effect on the growth of isografts from different benz(a)pyreneinduced rat sarcomas. The RNA was injected into the foot pads of rats bearing early growing tumor transplants.

Mannick and Egdahl,16 and Sabbadini

and Sehon<sup>24</sup> transferred allograft immunity with RNA extracted from the regional lymph nodes and/or spleens of animals undergoing active skin allowgraft rejection. Recipients of spleen cells which had been incubated with this RNA rejected specific skin grafts in an accelerated fashion. Similar results have been obtained in our laboratory.22 Rigby has prolonged the survival of mice bearing Ehrlich ascites tumors by administering syngeneic spleen cells previously incubated with RNA from the spleens of mice immunized with this tumor.23 We have observed a decreased incidence in the growth of tumor isografts in inbred mice following the administration of syngeneic spleen cells pre-incubated with heterologous RNA preparations; i.e., RNA extracted from the lymphoid tissues of guinea pigs immunized with the mouse tumor to be treated.21

A benz(a)pyrene-induced fibrosarcoma, designated BP-4, carried in C<sub>4</sub>H/FB (mammary tumor agent free) mice was used to immunize Hartley guinea pigs. Each pig received 0.5 ml. of a concentrated tumor cell suspension in complete Freund's adjuvant in each foot pad. An intraperitoneal injection, without adjuvant, was also given. After 10–14 days, the spleens, and axillary, popliteal and inguinal lymph nodes (sites of antigen processing) were excised and immediately frozen in dry ice. RNA was extracted as previously described.<sup>22</sup>

Cell suspensions were prepared from the spleens of normal C<sub>2</sub>H/HeN mice as previously described, and the spleen cells were then incubated in the RNA solutions at 37°C. for 20 minutes in a shaking water bath at a concentration of 10<sup>7</sup>–10<sup>8</sup> cells/ml. The cells were washed, counted and the concentration adjusted to 1-2×108 viable cells per ml. Normal spleen cells were also incubated with RNA extracted from guinea pigs immunized with a mixture of normal C<sub>8</sub>H lung, liver, kidney and spleen cells. As controls, RNA was prepared from the lymphoid tissues of pigs immunized with Freund's adjuvant only, and RNA extracted from pigs immunized with BP-4 was treated with 20 gm./ml. of ribonuclease for 15 minutes at 37°C. prior to incubation with spleen cells.

Normal C<sub>1</sub>H mice were divided into groups of approximately 30. Each mouse was given, on 2 successive days, intraperitoneal injections of 5-10×10<sup>7</sup> spleen cells which had been incubated in the RNA preparation designated for its group. In addition, I group of mice received normal C<sub>1</sub>H spleen cells which had not been incubated with RNA, and I group received no spleen cells at all. Mice in all groups received a subcutaneous inoculum of 10<sup>4</sup> BP-4 cells in the flank coincident with the first injection of spleen cells. All animals were observed for tumor development.

The results are depicted in Table II. Recipients of intraperitoneal injections of spleen cells incubated with RNA from guinea pigs immunized with BP-4 evidenced a statistically significant inhibition of tumor development when compared to untreated mice or to mice receiving spleen cells which had not been incubated with RNA. When RNA from pigs immunized with BP-4 was treated with ribonuclease, no inhibition of tumor development resulted. Groups of mice receiving spleen cells incubated with RNA from pigs immunized with Freund's adjuvant alone also exhibited no inhibition of tumor growth. Most interestingly, spleen cells incubated with RNA from pigs immunized with normal C<sub>2</sub>H tissues did not cause a statistically significant inhibition in the growth of BP-4 tumor isografts. This is evidence of at least partial tumor specificity, and is the principal reason for our belief that immunity to tumor specific transplantation antigens has been transferred to previously normal spleen cells by these 'immune" RNA preparations.

It is possible that incorporation of informational "immune" RNA by the spleen cells during incubation is responsible for the conversion of these normal lymphoid cells to immunoreactive cells. However, Gottlieb and others have submitted convincing evidence that there is persistence

TABLE II

DEVELOPMENT OF BP-4 TUMOR ISOGRAFTS IN C4H MICE FOLLOWING SUBCUTANEOUS INJECTION OF 104 TUMOR CELLS. EXPERIMENTAL MICE ALSO RECEIVED INTRAPERITONEAL INJECTIONS OF SYNGENEIC SPLEEN CELLS INCUBATED WITH INDICATED RNA PREPARATIONS. RESULTS DEPICTED ARE COMBINED FROM 3 SEPARATE EXPERIMENTS

	No. of Mice Developing Tumors		
Groups	Total No. of Mice in Group		
	No.	Per Cent	
Recipients of Spleen Cells Incubated with RNA from Guinea Pigs Immunized with: A. BP-4 tumor cells B. Normal C <sub>2</sub> H lung, liver, kidney and spleen C. BP-4 tumor cells (RNA-ase)* D. Freund's adjuvant only	19/58 26/49 35/54 36/46	32.7 P<0.01† 53 65 78	
Controls:  E. Challenge controls (no spleen cells)  F. Spleen cells not incubated with RNA	89/150 16/27	59·3 59	

<sup>\*</sup> These RNA preparations were treated with RNA-ase prior to incubation with spleen cells.

of antigen (probably processed antigen) bound to RNA extracted from immune lymphoid cells.4,10,11,12,14,15 An RNA-antigen complex might sensitize lymphoid cells in a more efficient fashion than antigen not bound to RNA. This, indeed, was demonstrated with the antigen hemocyanin by Askonas and Rhodes.4 Such RNA-antigen complexes of markedly increased immunogenicity have been termed "super antigens" by Friedman<sup>11</sup> and by Fishman and Alder.<sup>10</sup> If immunologic specificity resides within this processed antigen, it would seem that as long as the RNA does not alter antigenic specificity when binding to antigen, the species of origin of the RNA is not of prime importance. The role of RNA in such RNAantigen complexes may be analogous to that of the protein in a hapten-protein conjugate, where the nature of the protein carrier in no way alters the antigenic specificity of the haptenic moiety. Whatever the mechanism of action of "immune" RNA, the fact that treatment of our RNA extracts with RNA-ase inactivated the preparations, indicates that RNA is essential in this system of transferring immunity. Although the above experiments were

regional lymph nodes and spleens, Sabbadini and Sehon, working with immunity to transplantation antigens, have shown that "immune" RNA preparations from regional lymph nodes are significantly more effective (? contain more active RNA-antigen complexes) than is RNA from spleens.<sup>24</sup> We may speculate then that the regional lymph nodes process antigens released by a growing tumor and form RNA-tumor antigen complexes ("super tumor antigens"). These RNA-antigen complexes come into contact with immunocompetent cells which leave the lymph node and form clones of effector lymphocytes which populate the lymphoid organs and blood of the host and mediate specific immune responses against that tumor. This processing of antigen probably occurs quite early in the course of the growth of a single malignantly transformed cell into a clinically discernible tumor. By the time the surgeon or radiotherapist appears on the scene to treat the now clinically evident tumor, the clone or clones of specificially sensitized lymphoid cells are distributed systemically and excision or irradiation of the regional lymph

performed with RNA extracted from both

<sup>†</sup> P value by X2 with Yates' correction for this group when compared to control Groups E and F as well as to Groups C and D.

nodes will, at this time, not alter in any way the immunologic response of the host to his tumor.

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The authors wish to express their appreciation to the Editor of Cancer Research for permission to reproduce some of the figures originally published in that Journal.

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# THE PRESENT STATUS OF TREATMENT OF CERVICAL METASTASES FROM CARCINOMA ARISING IN THE HEAD AND NECK REGION\*

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TREATMENT of cancer in general has followed a pattern—an all out attack by a single modality and an eventual evaluation resulting in disenchantment followed by a renewed search for new or better methods of treatment, combinations of methods and innovations. The treatment of cervical metastases is following this pattern.

In the past surgery for treatment of cervical metastases consisted of local excisions and occasionally a more extensive procedure which was descriptively termed as "picking the berries out of a bun." In 1906, Crile<sup>5</sup> published his concept of en bloc dissection. Because of problems with anesthesia and postoperative mortality rates of about 10 per cent, the procedure was not accepted enthusiastically. About this time experiments with radium and roentgen rays suggested that this type of energy had a destructive effect on tumor cells. The prospect of curing cancer by irradiation was hailed as a promising sub-

Table I
INCIDENCE AND 5 YEAR SURVIVAL; CERVICAL
METASTASES ON ADMISSION

Primary Cancer	Incidence (per cent)	5 Year Survival (per cent)	
Anterior 1 tongue	45.0	16.2	
Base of tongue	70.0	24.0	
Floor of mouth	41.0	19.0	
Cheek	37.0	23.0	
Soft palate	47.0	17.0	
Tonsil	66.0	21.0	
Nasopharynx	71.0	15.0	

stitute for surgery. The early reports of results, however, failed to substantiate the expectations from irradiation in controlling metastases. With advances in anesthesia, better surgical technique, the use of blood replacement and the introduction of antibiotics, radical surgery had no further limitations. The concept of the radical neck dissection became a routine treatment of metastases in continuity with resection of the primary tumor and as an individual procedure.

A review of incidence of cervical metastases from cancer of the head and neck regions indicates the magnitude of the treatment problem (Table 1).

End results of surgical treatment point out a glaring contrast in the results in the group with cervical metastases on admission and that without metastases on admission (Table II). The rate of survival for the group without metastases is at least

TABLE II
FIVE YEAR SURVIVALS

	Over-all (per cent)	Metastases		
Primary Cancer		With (per cent)	Without (per cent)	
Anterior } tongue	43.0	16.2	55.0	
Base of tongue	26.0	24.0	48.0	
Floor of mouth	37.3	19.0	59.5	
Cheek	51.0	23.0	56.0	
Soft palate	41.0	17.0	68.0	
Tonsil	35.0	21.0	55.5	
Nasopharnyx	32.5	15.0	54.0	
	1	1	1	

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double or more than for the group with metastases.

The recurrence rate in the surgically treated neck is over 25 per cent. Beahrs and Barber<sup>2</sup> in 1962 reported a cervical recurrence rate of 26.5 per cent in 615 neck dissections. Rakov<sup>22</sup> reported a 26 per cent recurrence rate following radical neck dissection for cancer of the tongue, oral cavity and thyroid. Harrold<sup>13</sup> reported a recurrence rate of 28.9 per cent. Lindberg and Jesse<sup>17</sup> had a recurrence rate of 27 per cent in a group of 146 patients with cancer of the oropharynx, supraglottic larynx and hypopharynx.

These high recurrence rates for the radical neck dissection procedure are of major concern. The embolization of cancer cells in cervical lymphatics and lymph nodes from cancer of the head and neck regions is being studied in mice, rats, rabbits and dogs and observations have been made on humans. It is difficult, however, to relate much of these data to humans.

Fisher and Fisher' are of the opinion that "The lymph node is not as effective a barrier to tumor cells as formerly believed and that, if these findings are applicable to humans, the presence or absence of tumor in lymph nodes may be of little significance in the determination of lymphatic dissemination; however, since there is a better prognosis in patients with cancer when lymph nodes are not involved, it is generally believed that in the absence of nodal tumor lymphatic tumor cell dissemination has less likely taken place."

Recently, Baker and associates<sup>1</sup> at the Johns Hopkins Hospital have demonstrated in rabbits that "A radical neck dissection did not significantly reduce the variable barrier effect which was assumed by small regenerated lymphatic vessels and nodes in the dissected side of the neck or by intact nodes in the contralateral side of the neck."

Harris and Smith<sup>12</sup> in 1960 studied the problem of wound recurrence in a group of cases having cytologic studies performed on wound washings at the time of surgery and concluded that the recurrence rate for the group with positive surgical washings and the group with negative surgical washings showed no definite difference. Fisher et al.<sup>8</sup> in 1967 confirmed these findings.

In an effort to improve results and reduce the surgical recurrence rate for metastases, preoperative irradiation in varying dosages and time intervals has been and is being studied.

Goldman et al.<sup>10</sup> gave massive preoperative radiation therapy (5,500 r) for advanced carcinoma of the laryngo-pharynx and showed a 3 year survival of 74 per cent. Hora<sup>16</sup> observed regrowth of cancer cells within areas of cellular necrosis and fibrosis and concluded that radiation therapy alone rarely controls deposits of epidermoid carcinoma within the cervical lymph nodes.

Hanks et al.<sup>11</sup> reported that with megavolt radiotherapy for cancer of the nasopharynx the chance of controlling involved lymph nodes was identical with the ability to control the primary disease. In 69 patients with various other head and neck cancers associated with clinical lymphadenopathy (N<sub>2</sub> and N<sub>3</sub>) the 5 year survival was 26 per cent after use of radiotherapy alone. In 3 per cent, treatment failed because of inability to sterilize lymph node metastases when the primary lesion was controlled.

Lindberg and Jesse<sup>17</sup> reviewed the records of 146 patients with cancer of the oropharynx, supraglottic larynx and hypopharynx in whom a radical neck dissection alone was performed and had a 20 per cent failure rate. In a comparable group of 145 patients receiving radiation therapy (5,000 r minimum) either prior or subsequent to neck dissection the recurrence rate was 15.2 per cent. The greatest improvement was noted in N<sub>2</sub> and N<sub>3</sub> cases in which the failure rate was reduced from 32.4 per cent for surgery alone to 17.0 per cent.

Catlin and Strong<sup>4</sup> and Strong et al.<sup>24</sup> in a controlled prospective study from 1960 through 1964 reported a recurrence rate of 50 per cent in the group with proven positive neck lymph nodes treated by surgery

and a 30.9 per cent rate in the group receiving preoperative irradiation (2,000 r in 5 days). The differential of 19 per cent is impressive. The over-all recurrence rate was 33.1 per cent for surgery alone and 22.5 per cent for the treated group. They concluded "that low-dosage preoperative radiation therapy to the neck can reduce the incidence of recurrence at the site significantly."

Six or 8 months after irradiation tumor cell metastases are not infrequently observed to recur and grow and must be treated aggressively by surgery under more difficult conditions. In a recent case a patient with a squamous cell carcinoma of the pyriform sinus with cervical metastases was treated 22 years ago with orthovoltage therapy (5,400 r) to the primary tumor and neck followed by a left neck dissection 3 weeks later. A year and one-half later, metastases appeared in the contralateral neck (right) and a palliative radical neck dissection was performed. Tumor was found invading muscle and surrounding tissue and, for this reason, radon seeds were implanted into the involved tissues after the major portion of tumor was removed. Fourteen years later, a local excision of a metastaticlymph node from the submandibular region was performed in the contralateral side. Four years later another lymph node was found on the same side but because of the poor medical condition of the patient surgery was deferred. Finally 4 years later (February 1970) the lymph node which had increased markedly in size during the 4 years was removed under local anesthesia. At no time was there evidence of recurrence of the primary tumor, the presence of a second primary tumor or disseminated metastases. How do we explain the appearance of metastases 14 years later and now 22 years later? Is this evidence for containment of a tumor cell because of the marked radiation fibrosis which many years later, for some unknown reason, activates and overcomes the fibrous encapsulation but still remains localized without evidence of generalized metastases? Why does the tumor bed permit the tumor cell to survive and then suddenly release it into vigorous activity? What produces the change in the neck tissues—is it a change in enzyme production or is it an immunologic change in the host?

Considering the available experimental data, the incidence of metastases for the sites of origin and the difference in end results in the group with cervical metastases and that without metastases and the relatively high incidence of recurrence following a radical neck dissection we may ask the following: (1) Is the radical neck dissection adequate to avoid the risk of dissemination via lymphatics and lymphaticovenous pathways? (2) Are we spilling and leaving tumor cells in the wound during surgery, a fertile host field for takes (Fisher has shown that trauma favors the susceptibility to tumor cell takes)? (3) Is the elective neck dissection indicated in all cases of high incidence of metastases for a given site? (4) What has preoperative high voltage irradiation followed by radical neck dissection indicated so far? (5) How does one explain cervical metastases recurrence 10 to 20 years after presumably effective treatment of the primary cancer and the neck metastases? and (6) How do we explain the cervical metastases in the absence of a primary lesion (primary undetermined) which may reveal itself months or even many years later?

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#### EVOLUTION OF THE CLINICALLY NEGATIVE NECK IN PATIENTS WITH SQUAMOUS CELL CARCI-NOMA OF THE FAUCIAL ARCH\*

By ROBERT D. LINDBERG, M.D., HOWARD T. BARKLEY, Jr., M.D., RICHARD H. JESSE, M.D., and GILBERT H. FLETCHER, M.D. HOUSTON, TEXAS

A CONSIDERABLE controversy has ensued concerning the management of the neck in patients without palpable lymph nodes on admission. The policy at The University of Texas M. D. Anderson Hospital has been not to electively treat the entire neck in patients with faucial arch lesions. The purpose of this paper is to determine guidelines for the management of the neck at the time of initial treatment.

#### CLINICAL MATERIAL

The records of 227 patients with previously untreated squamous cell carcinoma of the retromolar trigone-anterior faucial arch and 80 patients with soft palate lesions treated from 1948 through 1965 were reviewed. Of these patients, 170 were clinically free of lymph node metastasis on admission (125 patients with primary lesions in the retromolar trigone-anterior faucial pillar and 45 with lesions in the soft palate). The percentage of patients presenting without evidence of cervical lymph node metastasis on admission according to the clinical stage of the primary is shown in Table 1.

The neck is divided into the following 5 areas (Fig. 1):

Area I —includes only the subdigastric (tonsillar, sentinel) lymph node at the angle of the jaw.

Area II —includes a field bounded posteriorly by a line bisecting the sternomastoid muscle, inferiorly by an imaginary line drawn at the upper border of the thyroid cartilage, and anteriorly by the anterior border of the submaxillary gland. Superiorly, it extends slightly over the lower border of the mandible. It has a common boundary with Area I posteriorly-superiorly.

Area III—that portion of the neck bounded anteriorly by the midline, posteriorly by a line bisecting the sternocleidomastoid muscle, superiorly by the upper border of the thyroid cartilage and inferiorly by the clavicle.

Area IV—includes the submental area

TABLE I
STAGE ON ADMISSION
Clinically No
(1948 through 1965)

Stage	RMT-AFP	Soft Palate
T <sub>1</sub> T <sub>2</sub> T <sub>3</sub> T <sub>4</sub>	28/31* (90%) 50/82 (62.5%) 35/82 (42.7%) 12/32 (37.5%)	16/19 (84,5%) 19/32 (59.5%) 7/20 (35%) 3/9 (33%)
Total	125/227 (55%)	45/80 (56.5%)

\* No cases/Total number of patients. RMT-AFP=retromolar trigone-anterior faucial pillar.

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from the point of the chin superiorly to the upper border of the thyroid cartilage inferiorly and has a common boundary with Area II laterally.

Area V — the entire posterior triangle of the neck.

The degree of the neck covered by external beam irradiation depends both on the anatomic site of origin and the size of the primary lesion. Early lesions of the retromolar trigone or high on the soft palate may be irradiated without covering any lymph nodes in the neck, whereas the tonsillar lymph node is always included in the irradiated field, even in patients with early lesions of the anterior faucial pillar. The tonsillar lymph node also is included in patients with lesions of the uvula because of its anatomic position. In general, as the size of the primary lesion increases, more of the neck is irradiated in order to obtain adequate coverage of the primary lesion. Thus, Area I is usually included in the primary field, while Area II is less often covered. The dose varies from 6,000 rads in 5 weeks to 7,000 rads in 7 weeks.

Patients having had a neck dissection or radiation therapy to Area III are considered to have had complete elective treatment to the neck.

The figures reported in this series refer to whether the neck of the patient has been free of cancer for 4 years or until his death. They do not imply that he is alive, free of the primary cancer, or distant metastasis.

#### RETROMOLAR TRIGONE-ANTERIOR FAUCIAL PILLAR

Of the patients with primary cancers of the retromolar trigone-anterior faucial pillar, 125 had no clinical evidence of cervical lymph node metastasis on admission. The primary lesion in 20 patients was treated surgically and irradiated in 101; 4 patients received combined radiation therapy and surgical excision.

In 5 patients, a neck dissection was done in continuity with resection of the primary

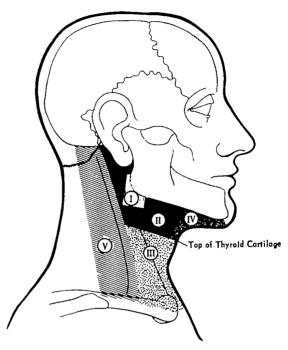


Fig. 1. Areas of possible radiation therapy. (Courtesy: Jesse, R. H., Lindberg, R. D., Barkley, H. T., and Fletcher, G. H.: Am. J. Surg. 9)

cancer (Table II). The cancer was controlled in 4 of these patients, while the fifth patient died with recurrent disease in both the primary site and the neck.

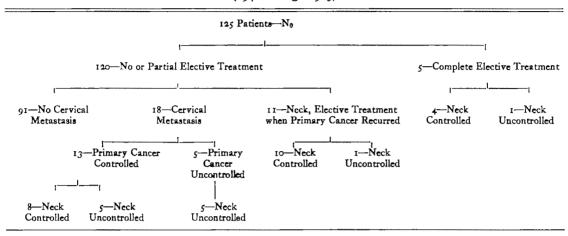
The remaining 120 patients with no or partial elective treatment to the neck are divided into 3 groups.

Group I consists of II patients who had recurrence of the primary lesion and were still clinically N<sub>0</sub>. These II patients had complete treatment to the neck with the primary recurrence; 7 patients were treated surgically, 2 were treated by radiation therapy, and 2 received combined therapy. The treatment was successful in 10 of the II patients; I patient died with cervical lymph node metastasis.

Group II is composed of the 9I (76 per cent) of the 120 patients who did not develop cervical lymph node metastasis. Area I was irradiated in 30 patients, Areas I and II in 39 patients; the remaining 22 patients had no elective neck treatment.

Group III is composed of the remaining 18 patients who developed metastatic

TABLE II
RMT-AFP
Clinically No
(1948 through 1965)



lymph nodes in the neck. These lymph nodes were located as follows: subdigastric, 10; submaxillary, 5; midjugular, 2; and low jugular, 1. Two of the 18 patients did not receive any neck irradiation; Area I was irradiated in 12 patients, and Areas I and II in 4 patients. Seven of the 18 patients had lymph node metastases either within or at the margin of the irradiated area of the neck. For analysis, Group III is subdivided, depending on the status of the primary lesion at the time when the cervical lymph node metastases became manifest clinically. Of the patients in Group III, 13 had control of their primary cancer when the metastatic cervical lymph nodes developed. The treatment of the neck in II of the 13 patients was a radical neck dissection, while I had radiation therapy and I had combined treatment. Eight of the 13 patients had control of their cancer in the neck, while in 5 the treatment proved unsuccessful and the patients expired with uncontrolled cervical lymph node metastasis.

The primary cancer was uncontrolled in the remaining 5 patients of Group III at the time the cervical lymph node metastasis became manifest. All 5 of these patients expired with cancer in both the primary site and the neck.

#### SOFT PALATE

Forty-five patients with primary cancers of the soft palate presented without clinical evidence of cervical lymph node metastasis. The primary cancers of 6 were treated surgically, and the remaining 39 by radiation therapy. In 2 of the 45 patients, the complete neck was treated in conjunction with the primary cancer, one by neck dissection and the other by radiation therapy (Table III). Both patients have remained free of disease.

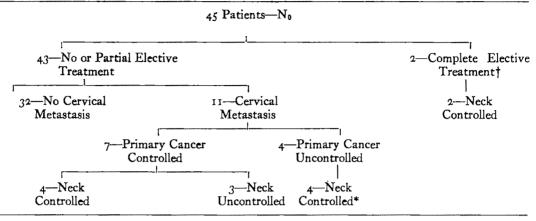
The remaining 43 patients who had no or partial elective treatment to the neck are divided into 2 groups. Group 1 is composed of 32 (74.5 per cent) of the 43 patients who did not develop cervical lymph node metastasis. Area I was irradiated in 11 patients, and Areas I and II in 11 patients; 10 patients had no elective treatment to the neck.

Group II consists of II patients who had clinically positive lymph nodes appear in the neck. The location of the new lymph node metastases was as follows: subdigastric, 8; submaxillary, 2; and low jugular, I. Of these II patients, 4 had no irradiation to the neck, 3 had Area I irradiated, and 4 had Areas I and II irradiated. The lymph node metastases developed within or at the margin of the irradiated areas in 5 cases.

TABLE III

SOFT PALATE

Clinically No
(1948 through 1965)



\* One patient died with distant metastasis.

† One patient had radical neck dissection, treated by radiation, therapy.

Group II is further subdivided according to the status of the primary lesion when the cervical lymph node metastases became manifest. In 7 patients, cervical lymph node metastases occurred at the time when the primary cancer was controlled clinically. Six of the 7 patients had radical neck dissections, and I was treated by radiation therapy. Three of the 7 patients expired with uncontrolled cervical cancer.

Four patients in Group II developed cervical lymph node metastases at the time their primary was known to be uncontrolled. In all 4, both the primary cancer and the disease in the neck were successfully treated.

#### DISCUSSION

Nineteen per cent (29/152) of those patients whose neck did not receive complete elective treatment at any time developed cancer in the neck, irrespective of the status of the primary lesion. If the primary lesion is uncontrolled at the time of lymph node metastasis, the neck may have been seeded either before treatment of the primary lesion or seeded from the recurrent cancer and no conclusion can be drawn concerning the management of the neck at the time of the initial treatment. If

the primary lesion is controlled at the time of appearance of the lymph node metastasis, the neck must have been seeded before treatment of the primary.

Southwick et al.,6 Kremen,5 and Beahrs et al.¹ found that 39.9, 43 and 25.3 per cent, respectively, of patients with oral cavity lesions having an elective neck dissection when their neck is clinically negative, actually have histologically positive lymph nodes at the time of initial treatment. Patients with faucial arch lesions have a higher incidence of positive lymph nodes on admission (45 per cent in our material) than those with primaries in the oral cavity (oral tongue, 35 per cent; floor of mouth, 31 per cent). One would expect a parallel higher incidence of subclinical lymph node metastasis.

Subsequent cancer in the neck is more likely to occur in patients with controlled lesions of the soft palate (7/39) than with retromolar trigone-anterior faucial pillar lesions (13/104). These low figures in primary lesions of the faucial arch in comparison to those published may lie in the fact that Area I in about one-third of the patients, and Areas I and II in an additional third are irradiated. When the lymph nodes in Areas I and II are included in the fields,

they usually receive 6,000 to 7,000 rads in 6 to 7 weeks. Berger et al.2 have shown that 4,500 to 5,000 rads in 5 weeks will sterilize at least 90 per cent of subclinical deposits of squamous cell carcinoma in the neck.

Five (4.8 per cent) of 104 patients with primary cancer of the retromolar trigoneanterior faucial pillar and 3 (7.7 per cent) of the 39 patients with soft palate primaries who were clinically N₀ on admission and who did not receive complete elective neck treatment died with subsequent uncontrolled cancer in the neck.

An analysis was done to find parameters which would allow us to detect those patients most likely to develop cervical lymph node metastasis. The number of patients developing metastatic lymph nodes was the same in all stages: T<sub>1</sub>, 16.2 per cent (7/43); T<sub>2</sub>, 18.5 per cent (12/65); T<sub>3</sub>, 10.2 per cent (4/39); and T<sub>4</sub>, 14.2 per cent (2/12). In T<sub>3</sub> and T<sub>4</sub> lesions, Areas I and II are usually irradiated. Since the frequency of lymph node metastasis on admission increases with T stage, this is indirect evidence that a greater incidence of subclinical disease in Areas I and II is sterilized in advanced primary lesions.

One of 16 patients with Grade 1 lesions, 17 of 81 with Grade 11, and 6 of 33 with Grade 111 developed cervical lymph node metastasis. Five of 22 patients in whom no histologic grade was recorded also ceveloped metastasis. Patients with Grade 1 lesions appear to have less risk of developing cervical lymph node metastasis. The remaining patients appear to have the same risk, regardless of the histologic grading of the tumor.

Treatment of the ipsilateral lower neck whether by surgery or radiation therapy should not influence the incidence of contralateral lymph node metastasis, as most contralateral metastases develop in the subdigastric area. Thus, only I of the I43 patients with no or partial elective treatment to the neck developed contralateral metastasis after new ipsilateral lymph nodes were treated and controlled. Con-

tralateral metastasis appeared in 2 additional patients who had complete elective treatment to one side of the neck; I was successfully treated.

The incidence of distant metastasis was reviewed to determine if it is increased by not electively treating the ipsilateral neck. One of 29 patients who subsequently developed cervical lymph node metastasis died with distant metastasis without cancer present above the clavicle. This would indicate that there is no correlation between distant metastasis and the appearance of new neck disease provided the neck is successfully treated.

Because of the fact that most metastatic lymph nodes develop on the margin of the irradiated field, our treatment policy has been slightly modified, to include Area I and most of Area II to at least 5,000 rads in 5 weeks. Areas III, IV, and V are not irradiated, since lymph node metastases rarely appear in these areas. If possible, part of the submaxillary gland is not irradiated in order to preserve the salivary function.

A 5.6 per cent incidence of cervical failure does not justify the disability of a radical neck dissection, manifested by scars, loss of muscle, and shoulder drop. Irradiation of the entire neck with 4,500 to 5,000 rads in 5 weeks in itself produces few complications. This additional irradiation, however, may preclude proper treatment of a second primary lesion.

#### SUMMARY

A review of 170 patients with squamous cell carcinoma arising in the faucial arch without evidence of lymph node metastasis on admission leads to the following conclusions:

- 1. Eight of 143 patients (5.6 per cent) who did not receive complete elective treatment to the entire neck at any time and whose primary cancer remained controlled died with cervical lymph node metastasis.
- 2. The 5.6 per cent of the patients cannot be identified by the size of the primary

lesion or by the degree of undifferentiation of the primary lesion.

- 3. As one would expect, the incidence of contralateral lymph node metastasis is not influenced by treating the ipsilateral lower neck.
- 4. The frequency of distant metastasis is not increased when the ipsilateral neck is not electively treated.
- 5. The sequelae of treating 94.4 per cent of the patients does not justify the potential salvage of the 5.6 per cent who might have been benefited by complete elective treatment of the ipsilateral neck.

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#### ELECTIVE IRRADIATION OF THE NECK LYM-PHATICS FOR SQUAMOUS CELL CARCINOMAS OF THE NASOPHARYNX AND OROPHARYNX\*

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DUFFY's had indicated in 1938 that neck metastases from nasopharynx and oropharynx cancers are not efficiently managed by primary radical neck dissection because of the diffuse lymphatic spread. Dancot and Blavier's electively irradiated 68 patients with tonsillar fossa primary cancers and reported only 1 instance of new nodal disease in the electively irradiated areas. Elective irradiation, as defined herein, indicates that the neck of a patient received a substantial dose of radiation in a clinically uninvolved area of the neck.

The present study differs from the previous review in that additional patients with squamous cell carcinoma of the palatine arch have been added. There is also a more detailed comparison between the group of patients who had elective irradiation to the whole neck with the group who had only part of the neck irradiated.

#### CLINICAL MATERIAL

The clinical material (Table I) consists essentially of patients with squamous cell carcinoma arising in the nasopharynx or oropharynx, with only 3 patients with malignant tumors of salivary gland origin arising in the base of tongue and 7 patients with unclassified carcinomas in the tonsillar fossa and nasopharynx.

Three groups of patients are excluded from the study:

- Patients who were primarily treated surgically.
- 2. Patients whose radiation field covered only the area necessary to treat the primary lesion.
- 3. Patients with palpable lymph nodes in all areas of the neck whose irradiation is, therefore, therapeutic rather than elective.

Those patients whose cancer at the primary site or whose original neck metastasis was not controlled are not used for comparison, since the purpose of this study is to determine the effectiveness of irradiation in preventing the development of gross disease from initial subclinical cancer in the uninvolved areas of the neck. The possibility of reseeding from the uncontrolled cancer would introduce a distorting factor.

The staging of neck disease on admission is as follows:

- N<sub>0</sub>—No clinical evidence of lymph node metastasis
- N<sub>1</sub>—Single lymph node metastasis less than 3 cm. in diameter
- N<sub>2A</sub>—Single lymph node metastasis larger than 3 cm. in diameter
- N<sub>2B</sub>—Multiple ipsilateral lymph node metastases
- N<sub>8A</sub>—Fixed lymph node metastasis
- N<sub>8B</sub>—Bilateral lymph node metastases.

Eighty-six per cent of patients with squamous cell carcinoma of the nasopharynx presented with nodal disease, with

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TABLE I	
CLINICAL MATERIAL BY ANATOMIC S	ITES
(1948–Dec. 1965)	

	Nasopharynx	RMT and AFP*	Soft Palate and Uvula	Tonsillar Fossa	Base of Tongue
No. of patients with elective irradiation to neck	145	170	52	137	158
Uncontrolled disease Primary Neck Primary+neck	40 35 4 I	35 4 5	13 9 2 2	36 25 3 8	60 45 2 13
No. of patients with control of initial disease	105	126	39	101	98

<sup>\*</sup> RMT and AFP=Retromolar trigone and anterior faucial pillar.

either bilateral or fixed lymph nodes in 48 per cent;<sup>1</sup> patients with base of tongue lesions had 77 per cent nodal disease on admission, with fixed or bilateral nodal disease in 35 per cent; patients with fossa lesions had 75 per cent nodal disease on admission, with 31 per cent fixed or bilateral.<sup>7</sup>

The topographic distribution of the neck lymph nodes is well documented.<sup>1,5,7</sup> The subdigastric lymph nodes or the high jugular lymph nodes are most commonly involved on the ipsilateral side. When contralateral nodal disease is present, once again the most common sites involved are the subdigastric lymph nodes. All the lesions of the nasopharynx and oropharynx share the characteristic that rarely (2 per cent for tonsillar fossa, 3 per cent for nasopharynx, and none for base of tongue) the submandibular or submental lymph nodes are involved unless there is initial massive neck disease.<sup>1,5</sup>

Whole neck irradiation is defined as irradiation of all the lymphatic areas of both sides of the neck with the exception of the anterior submaxillary and submental areas. The spinal accessory chains are not included for lesions of the faucial arch and base of tongue.

Partial neck irradiation means that a

variable amount of the lymph node bearing areas on either the ipsilateral or contralateral side, or both sides of the neck, is irradiated. Partial neck irradiation for tumors of the palatine arch may have included only a portion of the subdigastric lymph node area on the ipsilateral side.

Table II indicates the lymph node staging for the patients and indicates in each nodal stage whether they have had whole neck or partial neck irradiation. A preference for whole neck irradiation is evident as the amount of nodal involvement increases. Whole neck irradiation is used commonly for lesions of the nasopharynx, tonsillar fossa and base of tongue. While it is not shown on the Tables herein, there is no correlation between the staging of the primary lesions and the type of neck irradiation employed.

Table III shows, by anatomic sites, the role played by radical neck dissection in the management of neck disease.

#### TECHNIQUES OF TREATMENT

With 250 kv. it was difficult to deliver a radiotherapeutic dose to the entire neck, although it had been attempted at M. D. Anderson Hospital in patients with cancers of the nasopharynx, and in selected patients with base of tongue and tonsillar

TABLE II
DISTRIBUTION OF LYMPH NODE STAGING

_		N <sub>0</sub>	$N_1$	N <sub>2A</sub>	N <sub>2B</sub>	N <sub>2A</sub>	$N_{3B}$
RMT and AFP							
	WN	1	7	5	10	. 2	5
	PN	68	15	5 5	7	I	0
Soft palate							
and uvula	WN	· 4	6	1	2	1	2
	PN	16	3	1.	2	I	0
Tonsillar fossa		<u>.</u>				`	
	WN	10	11	10	13	10	9
	PN	15	4	4	10	5	0
Base of tongue							
	WN	12	13	10	8	4	25
	PN	12	5	I	3	4	I
Nasopharynx							
. • •	WN	12	14	14	21	8	34
	PN	ı ı	ò	Ī	0	0	0

RMT and AFP= Retromolar trigone and anterior faucial pillar.

WN - Whole neck.

PN = Partial neck.

fossa lesions. With 250 kv., irradiation of the neck areas was done with long fractionation with skin doses of 5,000 rads in 7 to 8 weeks. The dose to the lymph nodes ranged from 90 to 80 per cent of the skin dose.

After megavoltage became available, whole neck treatment, *i.e.*, irradiation of the entire neck on both sides, has been used routinely for patients with carcinoma of the nasopharynx, base of tongue, and tonsillar fossa, and also for patients with extensive

nodal metastases associated with lesions of the soft palate and retromolar trigoneanterior faucial pillar.

The techniques evolved through the years. Either with a cobalt 60 unit or a 22 mev. beam, the upper neck lymph nodes are usually included in the fields covering the primary lesion; however, for some of the anterior faucial pillar-retromolar trigone and soft palate lesions, the subdigastric area was only partially covered. When lesions of the retromolar trigone-anterior

TABLE III

INCIDENCE OF RADICAL NECK DISSECTION BY ANATOMIC SITES AND AMOUNT OF NECK IRRADIATED

	Nasoph	arynx	RMT ar	Soft Palate and Uvula		Tonsilla	r Fossa	Base of Tongue		
	No RND	RND	No RND	RND	No RND	RND	No RND	RND	No RND	RND
Partial neck Whole neck		o 7	83 15	13	20 12	3 4	35 50	3 13	21 53	5
Total	98	7	98	28	32	7	85	16	74	24

RMT and AFP-Retromolar trigone and anterior faucial pillar.

RND=Radical neck dissection.

faucial pillar and tonsillar fossa were treated with only a homolateral field, the opposite upper neck did not receive an adequate dose. Parallel opposing portals (2:1 or 1:1 loading) are used for tonsillar fossa and base of tongue lesions to cover the upper necks to the level of the hvoid bone (or thyroid notch), excluding the anterior submaxillary and submental areas. The spinal accessory chain is not covered routinely except for lesions of the nasopharynx4 and on the ipsilateral side for lesions of the tonsillar fossa. The lower neck is irradiated with a straight anterior split portal, shielding the larvnx. Initially the given dose to the lower neck field was 6,000 rads in 5 weeks, later on 5,000 rads in 4 weeks, and for the last 7 or 8 years, if no lymph nodes are palpable, 5,000 rads in 5 weeks. An additional 500 or 1,000 rads given dose is administered on 1 side or the 2 sides if massive disease is present in the upper neck(s).

The supraclavicular and posterior cervical triangle lymph nodes are beneath the skin and, therefore, the tumor dose is the same as the given dose; the lower and midjugular lymph nodes receive approximately 10 per cent less than the given dose, *i.e.*, about 4,500 rads tumor dose in 5 weeks.

Figure 1 shows the portals in a patient with an anaplastic squamous cell carcinoma of the right vallecula.

#### RESULTS

There are 3 clinical end points which have been evaluated: (1) new neck disease appearing in an unirradiated area; (2) new neck disease appearing in a lymphatic area partially included in the radiation fields, usually the subdigastric area; and (3) new neck disease appearing in an electively irradiated area.

Table IV tabulates the 3 types of new nodal disease appearing in the neck according to whether the patient received irradiation to the entire neck or only to part of it. In only 2 patients in whom the entire neck was irradiated did new cancer appear in the unirradiated submental area. Since this



Fig. 1. Patient in treatment position for the anterior lower neck field. The primary lesion was an anaplastic squamous cell carcinoma of the right vallecula with positive bilateral neck lymph nodes. (Courtesy: Fletcher, G. H. *Textbook of Radiotherapy*. Lea & Febiger, Philadelphia, 1966, p. 171.)

incidence is less than I per cent of the total group of patients, we feel justified in not routinely irradiating the submental area, since the alternative in the remaining 99 per cent of the patients would be an extremely dry mouth due to irradiation.

There is clearly a higher incidence of new cancer developing in patients undergoing only partial irradiation of the neck. As shown in Table v, only 7 of 277 patients having whole neck irradiation had new disease in the neck as compared with 22 of 185 patients having only part of their neck irradiated. Patients who died within 2 years (95 per cent of nodal disease appears within 18 months of initial treatment<sup>6,8</sup>), either from intercurrent disease or distant metastases, had not been exposed to the full

Table IV

CORRELATION OF NEW NODAL DISEASE WITH IRRADIATED NECK AREAS

	Whole Neck Treatment			Partial Neck Treatment			
	Failure			Failure			
Site	Number	Elec- tively Irradi- ated	Not Irradi- ated	Number	Elec- tively Irradi- ated	Margin- ally Irradi- ated	Not Irradi- ated
Nasopharynx Retromolar trigone-anterior	103	I	0	2	0	0	0
faucial pillar	30	1	0	96	2*	3	4§
Soft palate	16	ot	0	23	0	2	2
Tonsillar fossa	63	0	I	38	I	0	3
Base of tongue	72	3	I	26	0	3	2
Total	284	5	2‡	185	3	8	II

\* One patient with recurrence in lower neck following radical neck dissection was excluded.

† One patient with recurrence in the surgical scar of radical neck dissection was excluded.

‡ Submental disease.

§ One contralateral upper neck in a patient with T3-No lesion treated with wedge pair.

Two contralateral upper neck in a T2-N0 and T3-N2B lesions treated with a homolateral field only.

risk of developing new nodal disease, but if one excludes those patients, the statistical significance remains the same.

Table vi indicates that the majority of patients with new cancer appearing in the neck were patients originally staged N<sub>0</sub>, the majority of these patients having received partial neck irradiation.

Of the 8 patients who developed new cancer in an electively irradiated area, 3 were found to have less than a therapeutic dose of irradiation. One of these patients, treated with 250 kv., received an equivalent dose of less than 4,000 rads in 5 weeks. The 2 other patients were treated with a 2:1

Table V

CORRELATION OF NEW NODAL DISEASE BY TYPE
OF IRRADIATION TECHNIQUE

New Nodal Disease	Whole Neck	Partial Neck
Absent	277	163
Present	7	22
Total	284	185

P<.001.

and 3:1 loading, respectively, and developed cancer in the contralateral upper neck in areas to have received a calculated dose of 4,000 rads in 6 weeks. New cancer appeared in the neck of only 5 of the patients who received an elective dose of irradiation of at least 4,500 rads in 5 weeks on a 5 day a week treatment schedule.

Of the 29 patients in this series developing new cancer in the neck, 21 developed their disease within 18 months and only 4 of these patients survived an additional 2

TABLE VI

CORRELATION OF NEW NODAL DISEASE

WITH INITIAL NODAL STAGE

Site	No	$N_1$	N <sub>2A</sub>	$N_{2B}$	N <sub>2A</sub>	N <sub>3B</sub>
Nasopharynx Retromolar trigone- anterior faucial pillar	6*	2*	1*	1		1*
Soft palate Tonsillar fossa Base of tongue	3 2 4*	I	1*	1 3†	I	I

\* One failure in an electively irradiated area.

† Two failures in an electively irradiated area.

years; the remaining 8 patients developed their new cancer after 18 months, and 6 of them have had subsequent successful treatment. When new cancer appears in the neck prior to 18 months, it is usually a manifestation of diffuse spread of a cancer, whereas, when it appears late, it is likely to be an isolated metastasis.

#### DISCUSSION

From the data presented, one can conclude that whole neck irradiation reduces to 1.7 per cent the subsequent development of new cancer in the neck, whereas in 10.2 per cent of patients with partial neck irradiation, lymph node involvement appears in nonirradiated neck areas. The low incidence of new disease appearing in the neck of those patients whose whole neck was irradiated is even more striking when one remembers that whole neck irradiation was most often employed for those patients having more advanced initial neck disease and primary lesion in the nasopharynx, tonsillar fossa and base of tongue. One would expect a high probability of subclinical involvement of the remaining lymph nodes in patients with clinically positive first level lymph nodes. Cancer was present in the distal lymph nodes of 6 of 21 patients undergoing radical neck dissections for oral cavity lesions in whom the proximal lymph nodes were negative. 11 One would assume that such occult distant metastasis is more likely to be present in patients with oropharynx cancer, since these cancers are even more metastatically aggressive than oral cavity lesions.

A dose of 4,500 to 5,000 rads would not control clinically recognizable disease anywhere close to the 90 per cent figure. The success of eradicating possible subclinical disease with radiation doses lower than those necessary to cure clinically manifest cancer is attributable to the fewer number of cancer cells and the fact that the cells are well oxygenated.

Significant fibrosis does not develop in the area irradiated with 5,000 rads in 5 weeks with megavoltage. A number of patients had a baseline I<sup>181</sup> pick-up before and after whole neck irradiation to determine whether thyroid function was affected. There was no hypothyroidism in these particular patients.<sup>10</sup> However, hypothyroidism has developed in a few of the patients treated through the years, not included in the I<sup>181</sup> study, and the possibility of this complication must be kept in mind during the follow-up period.

#### SUMMARY

- 1. Eight of 469 patients (1.7 per cent) developed new nodal disease in an electively irradiated area.
- 2. Nineteen of 185 patients (10.2 per cent) with partial neck irradiation developed new nodal disease in a marginally irradiated or unirradiated area.
- 3. A tissue dose of 4,500 to 5,000 rads tumor dose in 5 weeks is proposed for the irradiation of elective areas. This dose produces no complications or even minor sequelae.
- 4. Whole neck irradiation is indicated for squamous cell carcinomas of the naso-pharynx, tonsillar fossa, base of tongue, and N<sub>2</sub> and N<sub>3</sub> of the palatine arch.

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# COMPARATIVE EVALUATION OF THE SEQUENTIAL USE OF IRRADIATION AND SURGERY IN PRIMARY TUMORS OF THE ORAL CAVITY, OROPHARYNX, LARYNX AND HYPO-PHARYNX\*

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THE choice between primary surgical excision or primary irradiation, or the sequential use of both disciplines, varies with the anatomic sites of the upper respiratory and digestive tract and the extension of the disease.

The choice of primary irradiation is based on:

- (1) A high percentage of control
- (2) Possible surgical salvage of the irradiation failures
- (3) Nonprohibitive incidence and severity of complications with their possible management.

The incidence of recurrences and their surgical management have been analyzed for several anatomic sites in previous papers. The purpose of this study is to review these 3 criteria by anatomic sites. The analysis is limited to the results of management of the primary lesions, either by primary irradiation or preoperative irradiation followed by planned surgical excision.

The policies and detailed techniques of management of the neck lymph nodes have also been published. § . 6,7,8 Either pre- or postoperative irradiation, depending upon the anatomic site of origin of the primary lesion, reduces the incidence of recurrence in the radically dissected neck and prevents the appearance of disease in the opposite neck.

#### CLINICAL MATERIAL

All patients treated are included, even those treated palliatively for advanced lesions either at the primary site or in the neck. Table I shows the incidence of irradiation failures and their surgical management by anatomic sites. It would have been desirable to produce tables of T<sub>1</sub> through T<sub>4</sub> but they would have been too complex and too numerous for the purpose of this paper, which is to give an over-all comparative view of the place of primary irradiation for squamous cell carcinoma of all the anatomic sites of the upper respiratory and digestive tracts.

Surgical excision of irradiation failures in very advanced lesions is less likely to be possible; also uncontrolled neck disease or distant metastases may be a contraindication to excise a resectable recurrence at the primary site.

### TIME OF RECURRENCE OF IRRADIATION FAILURES SURGICALLY EXCISED

With the exception of the vocal cords, 95 per cent of the recurrences appear before 2 years. Approximately 25 per cent of vocal cord tumor recurrences appear between 2 and 5 years, possibly explained by the fact that vocal cord cancer is often associated with leukoplakia and/or in situ carcinomas so that a new disease appears after the treatment of the initial one.

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 $\begin{tabular}{ll} \textbf{Table I}\\ \textbf{Incidence of failures and their surgical management by anatomic sites}\\ \textbf{1948-1965}\\ \end{tabular}$ 

(3 yr. minimum to unlimited follow-up)

	No. of Patients	No. of	Surgery for Irradiation Failures			
Anatomic Sites	Treated by Irradiation	Irradiation Failures	No.	Disease above Clavicle	DM	
Anterior of Tongue Floor of Mouth Lower Gum Buccal Mucosa Hard Palate Upper Gum	225 179 42 85 4	77 40 19 21 2	35 21 10 11 1	13 5 3 1*	4 I I —	
Retromolar Trigone—Anterior Faucial Pillar Soft Palate—Uvula Tonsillar Fossa Base of Tongue Pharyngeal Walls	180 71 127 159 101	40 13 29 60 48	26 7 7 16	6 3 2† 7 3	I I I 4	
Vocal Cords Supraglottic Hypopharynx—Pyriform Sinus Hypopharynx—Pharyngeal Wall	338 115 46 29	53 37 15 8	45 23 4 3	6 4 2 1	2 3 1	

\* Postoperative death.

† 1 case recurred 34 months, living with disease at 38 months. DM=Distant Metastases.

The number of recurrences developing at the primary site after 5 years is low.

These recurrences are likely to be new primary lesions. This is because of the incidence of multiple primary lesions on the mucous membrane of the upper respiratory and digestive tracts which is, depending upon the anatomic site, of the order of 5 to 15 per cent in the M. D. Anderson Hospital material.

#### ORAL CAVITY

Anterior Two-Thirds of the Tongue and Floor of Mouth. Squamous cell carcinomas of the anterior two-thirds of the tongue have been treated by primary irradiation except when they were very early lesions or lesions located close to the tip of the tongue or on the dorsum of the tongue or when there were associated conditions such as alcoholism and/or heavy smoking. The incidence of failure is approximately 35 per

cent. Half of these recurrences were surgically excised with a 70 per cent incidence of freedom from disease above the clavicle.

The choice of primary treatment for floor of mouth lesions is subtle. Lesions of the floor of the mouth are more readily controlled by irradiation than those of the anterior two-thirds of the tongue. The rate of failure is 20 per cent, half of those surgically excised: of 21 patients with a resected recurrence, only 5 died with disease above the clavicle.

Gums, Buccal Mucosa and Hard Palate. Lesions of the upper gum and hard palate are as a rule treated surgically because of the difficulty of assessing involvement of the floor of the nose and/or of the antrum. Those of the buccal mucosa and lower gum are often associated with leukoplakia with a tendency to multiple primary lesions on the gum and the buccal mucosa. Early

lesions of the lower gum are best excised because of the wearing of dentures. The middle-sized lesions of the buccal mucosa and the unresectable infiltrative lesions are treated by radiotherapy; the lesions of the lower gum with saucerization but without frank bone invasion can be treated by irradiation; the massive lesions are managed palliatively. Because of the selectivity shifted to advanced stages, there is a rather high recurrence rate. Half of the recurrences of the buccal mucosa and lower gum were surgically excised, with few patients dying with disease above the clavicle.

#### OROPHARYNX

Tonsillar Area. There is a good control rate of the lesions of the soft palate, retromolar trigone-anterior faucial pillar and tonsillar fossa. Many of the recurrences of palate or anterior faucial pillar-retromolar trigone lesions can be surgically excised with good control of the disease, whereas few irradiation failures of the tonsillar fossa can be surgically salvaged. In addition to being less accessible, as they are usually located on the pharyngeal walls, the recurrences of tonsillar fossa lesions are often associated with extensive neck disease or distant metastases.

Base of Tongue. The incidence of failure is approximately 37 per cent; only a small percentage of such lesions can be excised. In addition to the difficulty of excising a base of the tongue recurrence which often involves pharyngeal walls, there is also the difficulty of extensive neck disease as well as distant metastases which may be a contraindication to excise a locally resectable recurrence.

Pharyngeal Walls. This site of disease has the highest incidence of failure with the lowest surgical salvage rate. For these reasons there has been a trend in the last decade to prefer primary surgical excision to radiation therapy.

#### LARYNX

Lesions limited to the cords or those extending beyond the cords with partial motility are treated by irradiation. The control

rate is 90 per cent if the lesion is limited to the cords; the control rate is 75 per cent for those extending beyond the cords. Of the 53 failures, 45 were surgically excised; 8 patients refused laryngectomy despite a resectable recurrence. Only 6 patients died with disease recurrent above the clavicle.

Exophytic lesions of the supraglottic structures, *i.e.*, epiglottis, aryepiglottic folds, and false cords, are treated by primary irradiation. The lesions of the suprahyoid epiglottis, even when more advanced, are also irradiated. Patients with unresectable disease are treated palliatively.

Of 37 failures after irradiation, 23 were in T<sub>1</sub>, T<sub>2</sub>, T<sub>3</sub> lesions and 14 in T<sub>4</sub> lesions. Fifteen recurrences were not managed by surgical excision because laryngectomy was refused, or because of unresectable disease, distant metastases and miscellaneous reasons. Seventeen of 23 failures in T<sub>1</sub>, T<sub>2</sub>, T<sub>3</sub> had laryngectomy with 14 successes. Only 5 of the 14 T<sub>4</sub> failures had laryngectomy. There were 5 successes.<sup>4</sup>

Hypopharynx. Only a few of the pyriform sinus and hypopharyngeal wall lesions are detected early and are suitable for primary irradiation. Some lesions are irradiated for palliation when unresectable either at the primary site or in the neck. Rarely are failures amenable to surgical salvage.

### HIGH-DOSE PREOPERATIVE IRRADIATION

Table II shows the results of high-dose preoperative irradiation.

This group is composed of patients with advanced lesions, usually infiltrating or invading bone. They received 5,000 rads in 5 weeks or even 6,000 rads in 6 weeks to the primary lesion and sometimes also the neck lymph nodes, followed by a composite operation 6 to 8 weeks later. The results are good for oral cavity and oropharyngeal lesions with the exception of the tonsillar fossa. By and large, the lesions suitable for the sequential procedure are in the same anatomic sites as those where surgical excision of irradiation failure is often possible and successful. The anatomic location and

Table II

HIGH-DOSE PREOPERATIVE IRRADIATION
1948–1965

(3 yr. minimum to unlimited follow-up)

Anatomic Sites	No. of Patients	Disease above Clavicle	DM
Anterior 3 of Tongue	IO	3	
Floor of Mouth	8	2	I
Lower Gum	11	2	2
Buccal Mucosa	6	I	1
Hard Palate	0	<u> </u>	
Upper Gum	I		
Retromolar Trigone—Anterior Faucial Pillar	10	I	I
Soft Palate—Uvula	2	_	<del></del>
Tonsillar Fossa	10	6*	
Base of Tongue	7	2	2†
Pharyngeal Walls	Ī	I	· .
Vocal Cords	I	_	
Supraglottic	4	3	NAME OF THE PARTY.
Hypopharynx—Pyriform Sinus	3		2
Hypopharynx—Pharyngeal Wall	10	3	3

\* 1 case received 5,000 rads tumor dose preoperative. No surgery due to poor physical condition. Died of disease at 12 months.

† I case received 5,000 rads tumor dose preoperative. No surgery due to lung metastasis. Died of disease at 7 months.

DM - Distant Metastases.

the extent of neck disease is favorable for lesions in these anatomic sites.

The high-dose preoperative irradiation is fraught with severe complications when extensive resection of the pharynx necessitates skin grafting. It is preferable to perform the surgical procedure first, followed by postoperative irradiation.

### LOW-DOSE PREOPERATIVE IRRADIATION

Sixteen patients with lesions of various anatomic sites were treated preoperatively with 2,000 rads in 5 treatments. The numbers are too small to draw conclusions, but it seems that 2,000 rads given preoperatively has little merit in lesions of borderline operability.

#### RESECTION FOR NECROSES

Bone exposure proceeding to osteitis or persistent pain necessitates segmental resection of the bone. The resection is done intraorally resulting in little disfigurement. There are also a few soft tissue necroses

requiring resection. The relief of pain is immediate and the control of the disease has been excellent, ruling out the so-called supralethal effect (Table III). It justifies radicalism in irradiation because the tumor can be controlled and these painful complications can be successfully managed. The technique is important in the incidence and severity of complications; e.g., in lesions of the tonsillar area subjected to cobalt 60 teletherapy, one homolateral portal or wedge pair technique results in more bone necroses necessitating resections than the parallel opposing portal technique.5 The bone receives a higher dose with the first 2 techniques, but with parallel opposing portals dryness is greater.

The incidence of bone necroses necessitating resection is higher for the floor of the mouth than the tongue, as would be expected because of the proximity of bone.

In the group with laryngeal lesions there have been I laryngectomy and I tracheotomy for necrosis or massive edema after irradiation of the supraglottic structures.

Table III

radiation necroses surgically treated

1948–1965

(3 yr. minimum to unlimited follow-up)

Anatomic Sites	No. cf Patients Treated by Irradiation	No. of Necroses Surgically Treated	Disease above Clavicle
Anterior # of Tongue	225	15	I
Floor of Mouth	179	16	2
Lower Gum	42	3	I
Buccal Mucosa	85	4	—
Hard Palate	4	0	
Upper Gum	9	0	
Retromolar Trigone—Anterior Faucial Pillar	180	16	I
Soft Palate—Uvula	71	I	
Tonsillar Fossa	127	10	I
Base of Tongue	159	IO	I
Pharyngeal Walls	101	I	I
Vocal Cords	338	5	I
Supraglottic	115	I	
Hypopharynx—Pyriform Sinus	46	0	
Hypopharynx—Pharyngeal Wall	29	0	_

#### CONCLUSION

A comparative review of the percentage of failure of irradiation for the various anatomic sites of the mouth and throat gives guidelines for primary radiation therapy on the basis of incidence of local control and the possibility of surgical correction of irradiation failures as well as the correction of complications.

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#### TELECOBALT THERAPY FOR CARCINOMA OF LARYNGOPHARYNX\*

By C. M. LALANNE, Y. CACHIN, G. JUILLARD, and R. LEFUR VILLEJUIF, FRANCE

FROM 1955 to 1963, 715 cases of cancer of the laryngopharynx have been treated with telecobalt at the Institut Gustave Roussy. The general distribution of these patients is shown in Table 1. Fifteen patients presenting with distant metastases and 14 with inadequate information have been excluded. There remain 686 cases available for the present study.

The cancers of the patients are divided into 3 groups: (1) of larynx; (2) of hypopharynx; and (3) of ridge or epilarynx. By ridge we mean the frontier separating intrinsic larynx from hypopharynx. It is made of the brim of the epiglottis, aryepiglottic folds and arytenoids.

The survival rate at 5 years is 46 per cent in cancer of the larynx and only 11 per cent in cancer of the hypopharynx. With a survival of 20 per cent, ridge lesions occupy an intermediate position, nearer to hypopharynx (Table II). Some of the hypopharynx cases have already been studied and the method of irradiation described elsewhere.

Based on the treatment policy, the 8 years, 1955–1963, can be divided into 2 periods, each corresponding to a different treatment policy.

During the first period, 1955-1960, cancers of the laryngopharynx, whatever their origin, received telecobalt therapy as the primary treatment. The dose delivered to the primary tumor was 6,000 r, with a weekly dose of 800 r and then 1,000 r. Except in vocal cord cancers, the lymph nodes in one or both sides of the neck were irradiated and received a lower dose than the primary tumor, because a radical neck dissection was planned after telecobalt therapy for cases presenting with palpable lymph nodes. The recurrent primary tumors were operated, as well as the lymph nodes if necessary. A few cases, less than 10 per cent, did not receive telecobalt therapy and are excluded from this review. They were selected for operation by the surgeon first seeing the patients and eventually received postoperative conventional radiotherapy.

The second period, 1960–1963, was characterized by the organization of a steady cooperation between the surgeon and the radiotherapists, who together made all therapeutic decisions. Treatment was chosen according to the origin of the cancer.<sup>4</sup>

Larynx cancer treatment was conservative and designed for curing the disease and

Table I

Telecobalt therapy of cancer of the laryngopharynx

1955-1963

General Distribution

Origin	Total No.	Distant Metastasis	Inadequate Information	No. Under Study
Larynx (intrinsic)	237	2	0	235
Ridge (epilarynx)	168	3	4	161
Hypopharynx (extrinsic)	310	10	10*	290

<sup>\*</sup> One alive at 5 years.

<sup>\*</sup> Presented at the Fifty-first Annual Meeting of the American Radium Society, Philadelphia, Pennsylvania, April 27–30, 1969. From the Institut Gustave Roussy, Villejuif, France.

TABLE II

TELECOBALT THERAPY OF CANCER OF
THE LARYNGOPHARYNX
1955-1963
5 Year Survival Related to Origin

Origin	No.	Per Cent
Larynx	235	46
Ridge	161	20
Hypopharynx	290	11
All sites	686	25

preserving normal speech and breathing. Lesions suitable for a partial laryngectomy, i.e., mobile vocal cord cancers, were operated by simple or extended cordectomy. Good prognosis cases did not receive telecobalt therapy and are consequently excluded from this review. All other cases needing a total laryngectomy were treated first by telecobalt. At 4,000 r, the final decision was made at the joint clinic run by the surgeon and radiotherapist. Radioresistant operable lesions had total laryngectomy followed by another dose of 4,000 r. Radiosensitive operable and all inoperable lesions received complete telecobalt therapy, in up to 6, 7 or more weeks (1,000 r weekly).

Ridge lesions were treated by following the same lines. However, special mention should be made of the anterior lesions of the ridge and also of the anterior lesions of the supraglottic larynx. Their anterior location permitted a horizontal supraglottic laryngectomy, preserving the arytenoids and the cords, which was extended if needed to the base of the tongue. A 4,000 r dose of telecobalt therapy was given before and after the operation. The procedure, at first cautiously applied, became progressively the usual treatment of all anterior operable lesions.

Cancers of the hypopharynx received during the first period the treatment already described for the larynx. In 1960, when close cooperation between the surgeon and the radiotherapist was established, it was decided to use preoperative telecobalt

therapy at a dose of 4,000 r, pharyngolaryngectomy and postoperative telecobalt therapy at the same dose level of 4,000 r. The interval between preoperative irradiation and operation was usually from 2 to 4 weeks.

Lymph node dissection was always added to surgery of the primary tumor for lesions of any origin, when found necessary.

Table III gives the 5 year survival of all consecutive cases treated during the 2 periods according to the 2 different policies. No patient has been omitted, not even those receiving doses under 3,000 r, because of their poor general condition. Also, 14 patients without follow-up have been included in the deceased group. Survival of all cases is equal for the 2 periods: 25 per cent. In cancer of the larynx, no significant difference is observed between the 2 chronologic series: 47 per cent in the first period and 44 per cent in the second. Some cases operated at first are not included in these results. During the second period these cases represent 22 per cent of all cancer of the larynx cases and have a 5 year survival rate of 75 per cent. If included, they would improve the total survival rate of the cancer of the larynx patients from 44 per cent to 50 per cent.2 For cancer of the hypopharynx, the results are also equal: 12 per cent on one side and 10 per cent on the other. It is in ridge cancers that the greatest

Table III

TELECOBALT THERAPY OF CANCER OF
THE LARYNGOPHARYNX
1955-1963

5 Year Survival Related to Origin and Treatment Time

Period	1955–1960		1955-1960 1960-19		-1963
Origin	No. Per Cent		No.	Per Cent	
Larynx Ridge Hypopharynx	117 75 138	47 14 12	118 86 152	44 24 10	
Total	330	25	356	25	

TABLE IV

#### TELECOBALT THERAPY OF CANCER OF THE LARYNGOPHARYNX 1960-1963

5 Year Survival Rate Related to Estimate of Origin

Survival Rate (optimistic)	Origin	Survival Rate (pessimistic)
46%	235 larynx	04
~	161 larynx	35%
14%	290 hypopharynx	11%

difference is observed: the survival rate rises from 14 per cent in the first to 24 per cent in the second period. This improvement is probably due to a more frequent use of partial laryngectomy during the second period.

Comparison of the 2 series would necessitate a very long analysis; therefore, it is better to point out only some particular observations.

(A) The first observation is in regard to the T. N. M. classification. T. N. M. classification was used as soon as it was proposed by the I. U. C. C. It divides laryngopharynx into larynx and hypopharynx; however, the distribution of the ridge lesions between larynx and hypopharynx is somewhat arbitrary, because they infiltrate in both directions, internal and external.

Table V

CANCER OF THE LARYNX
1955–1963
5 Year Survival Related to Method of
Treatment and T Stage

Method of Treatment		obalt rapy	cobalt T	ned Tele- Therapy, y, Tele- Therapy
	No. Per Cent		No.	Per Cent
T <sub>1</sub> +T <sub>2</sub> T <sub>3</sub> T <sub>4</sub>	85 40 9	59 25 11	35* 36 8	49 39 37

<sup>\*</sup> Simple and extended cordectomies excluded.

TABLE VI

#### cancer of the ridge 1955-1963

5 Year Survival Related to Method of Treatment and T Stage

Method of Treatment	Telecobalt Therapy		cobalt T Surgery	ed Tele- Therapy, 7, Tele- Therapy
	No.	Per Cent	No.	Per Cent
T <sub>1</sub> +T <sub>2</sub> T <sub>3</sub> T <sub>4</sub>	34 29 45	4 <sup>I</sup> 14 11	7 10 21	28 20 23

Table IV shows the difference in survival rate produced by including the ridge cancers in one group or the other. Added to hypopharynx, they give an optimistic view of the situation: 46 per cent 5 year survival for patients with cancer of the larynx and 14 per cent for the hypopharynx. Added to larynx they give on the contrary a pessimistic outlook: 35 per cent for patients with cancer of the larynx and 11 per cent for the hypopharynx. This suggests that ridge cancers must be recognized as a third group between larynx and hypopharynx cancers, if homogeneous groups of cases are to be obtained; also, that reports on larynx or hypopharynx must always be presented

TABLE VII

CANCER OF THE HYPOPHARYNX\*

1955-1963
5 Year Survival Related to Method of

Treatment and T Stage

Method of Treatment	Telecobalt Therapy  No.   Per Cent		cobalt 7	ed Tele- Therapy, 7, Tele- Therapy
			No.	Per Cent
T <sub>1</sub> +T <sub>2</sub> T <sub>3</sub> T <sub>4</sub>	44 76 87	18 13 2	10 30 10	20 23 10

<sup>\*</sup> Eighteen posterior wall lesions excluded (II per cent 5 year survival).

Table VIII

CANCER OF THE LARYNX
1955–1963

5 Year Survival After Telecobalt Therapy as Primary Treatment

Period	1955–1960		Period 1955-1960		1960	-1963
Telecobalt Therapy	No.	Per Cent	No.	Per Cent		
Alone Lymph Node Dissection (Combined or	51	46	49	45		
for Recurrence) Surgery (for Recurrence) on Primary	11	55	2	100		
Tumor±Lymph Node Dissection	12	33	9	44		

as a part of the total group of laryngopharynx.

(B) The second observation concerns the methods of treatment. Considering both series together, 2 methods of treatment were used:(a) telecobalt therapy; and (b) surgery with pre- and postoperative telecobalt therapy. For T<sub>I</sub> and T<sub>2</sub> larynx lesions, telecobalt therapy secured 59 per cent 5 year survival and the alternative treatment 49 per cent. For T<sub>3</sub> lesions, the figures were 25 and 39 per cent respectively (Table v). The same trend was observed for ridge (Table vi) and hypopharynx (Table vii) lesions. For instance, 11 per cent of the T<sub>4</sub> ridge cases are living at 5 years after telecobalt therapy, as compared to 23 per cent after combined radiation-surgery. In small lesions, T<sub>I</sub> and T<sub>2</sub>, telecobalt therapy appears as effective as combined treatment, but on larger lesions, T3 and T4, the surgical treatment combined with radiotherapy gives better results. This observation is in agreement with the conclusions drawn by others from the study of large series.<sup>7-9</sup>

Three points about these methods of treatment deserve special consideration:

(1) Telecobalt therapy does not mean that patients just received radiation. Table VIII shows that out of 74 cases of cancer of the larynx treated during the first period, 11 had a lymph node dissection sometime during the course of the disease and 12, or 16 per cent, had a total laryngectomy for recurrence. These post-telecobalt therapy laryngectomies secure a 5 year survival rate of 38 per cent. The rate of salvage is lower for other sites: about 20 per cent for ridge (Table IX) and less than 10 per cent for hypopharynx (Table X) cancers.

(2) The choice of treatment depends on many factors (Table XI). In cancer of the hypopharynx, seen during the second per-

Table IX

cancer of the RIDGE (EPILARYNX)

1955-1963
5 Year Survival After Telecobalt Therapy as Primary Treatment

Period	1955–1960		1960-1963	
Telecobalt Therapy	No.	Per Cent	No.	Per Cent
Alone Lymph Node Dissection (Combined or	41	14	43	28
for Recurrence) Surgery (for Recurrence) on Primary	10	10	3	33
Tumor±Lymph Node Dissection	9	ıı	2	50

## Table X cancer of the hypopharynx 1955–1963

5 Year Survival After Telecobalt Therapy as Primary Treatment

Period	1955–1960		1960-1963	
Telecobalt Therapy	No.	Per Cent	No.	Per Cent
Alone Lymph Node Dissection (Combined or	65	22	95	5
for Recurrence)	24	12	0	· ·
Surgery (for Recurrence) on Primary Tumor±Lymph Node Dissection	28	7	0	

iod, only 29 per cent, less than one-third of the patients, could receive the designed radiation-surgery treatment. Extension of the lesion in 32 per cent and refusal of mutilation in 11 per cent were the main obstacles to surgery. Therefore, radiation therapy must still play an important and difficult role in laryngopharynx cancers.

(3) Radical surgery after telecobalt therapy is followed by a high incidence of complications. This incidence is correlated with the type of surgery (Table XII). For instance, dramatic postoperative carotid hemorrhage occurs in 2 per cent of horizontal partial laryngectomies, in 7 per cent of total laryngectomies and in 11 per cent of pharyngolaryngectomies. Lymph node dissection makes apparently no difference. The radiation dose administered before surgery is also an important factor (Table

Table XI

CANCER OF THE HYPOPHARYNX
1960–1963

Primary Choice of Treatment

I. Preoperative Telecobalt Therapy,	
Surgery, Postoperative	
Telecobalt Therapy	29%
II. Telecobalt Therapy	
Extension of Tumor or/and	
Involved Lymph Nodes	32%
Poor General Condition	9%
Refusal of Surgery	11%
Good Regression at 4,000 r	8%
Indeterminate	4%
III. Other Treatment	7%

xIII). Postoperative carotid hemorrhage was observed in 3 per cent of cases after 4,000 r, in 6 per cent after 6,000 r and 25 per cent after 7,000 r or more. Adding both factors in the latter group of very high doses, it occurred in 15 per cent of larynx recurrences against 50 per cent of hypopharynx recurrences.

(4) The last observation worthy of mentioning here concerns the curative radiation dose. Table xiv shows the relationship between tumor dose and 5 year survival. It is interesting to note that the lowest dose producing 5 year survival was 4,000 r, at least for cancers of the larynx and ridge.

Over 4,000 r, cure rate increased with increasing dose. This is evident in larynx lesions: 44 per cent for the middle dose of 4,500 to 6,400 r (in fact 6,000 r); and 51 per cent for the high dose of 6,500 r or more. The same observation can be made for the hypopharynx: 8 per cent for the middle dose; and 14 per cent for the high dose. For ridge lesions, the correlation is confused, because of the particular selection of the cases distributed in the different dose groups. However, it can be said, from our experience, that the range of curative radiation dose appears very large: a few cases are cured with 4,000 r; and many are not cured with 8,000 r. The high radiosensitivity of some lesions is confirmed by the review of 139 cases operated after receiving 4,000 r: 22 per cent of tumors were found histologically destroyed (no tumor cells or disorganized sequelae) on careful examina-

# Table XII PREOPERATIVE RADIOTHERAPY OF CANCER OF THE LARYNGOPHARYNX 1960–1963

Surgical Complication Rate Related to Type of Surgery

Complications	Horizontal Supraglottic Laryngectomy (73 cases)	Total Laryngectomy (59 cases)	Total Pharyngo- laryngectomy (96 cases)	Without Lymph Node Dissection* (135 cases)	With Lymph Node Dissection (93 cases)
Fistula Carotid	13%	59%	80%	40%	72%
Hemorrhage	2%	7%	11%	8%	6%

<sup>\*</sup> Most of the horizontal supraglottic laryngectomies were performed without lymph node dissection.

# Table XIII PREOPERATIVE RADIOTHERAPY OF CANCER OF THE LARYNGOPHARYNX 1960–1963

Surgical Complication Rate Related to Radiation Dose

Complications	Total (228 cases)	Approximately 4,000 r (142 cases)	Approximately 6,000 r (50 cases)	7,∞∞ r (36 cases)
Fistula Carotid Hemorrhage	53% 7%	44% 3%	46% 6%	72% 25%
		Surgery as a part of planned treat- ment	Surgery if recurrence therapy	occurs after radio-

# Table XIV TELECOBALT THERAPY OF CANCER OF THE LARYNGOPHARYNX 1955–1963 5 Year Survival Rate After Telecobalt Therapy Related to Dose on Primary Tumor

D	<	3,000	3,00	3,000-4,400		4,500-6,400		≥6,5∞	
K	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	
Larynx	I	0	II	27	43	44	55	51	
Ridge	6	0	7	28	34	20	52	21	
Hypopharynx	7	0	23	0	62	8	95	14	

tion of multiple sections of the specimen. The radiosensitivity did not correlate with the origin nor with the extension of the tumors. However, there was a correlation between radiosensitivity and survival: 61 per cent at 3 years in radiosensitive against 38 per cent in radioresistant tumors. This suggests the predominant role of preoperative radiotherapy, or the hypothesis that

cure is linked to some specific characteristic of the patient, among which is radiosensitivity.

Over 6,000 r, the cure rate increases very slowly with increasing dose, and the dose giving statistically the best chances of cure lies between 6,500 and 7,500 r. Of course, this general statement must be adjusted to the site of the primary tumor. Mobile

lesions of the vocal cord should not receive, for instance, doses over 5,500 r, with the fractionation used  $(5 \times 200 \text{ r or } 4 \times 250 \text{ r per week})$ .

#### SUMMARY

- 1. In small lesions, T1 and T2, of the laryngopharynx, telecobalt therapy gives as good results as the combination of surgery and pre- and postoperative telecobalt therapy.
- 2. On the other hand, in larger lesions, T<sub>3</sub> and T<sub>4</sub>, surgery supplemented by radiotherapy seems to be the best treatment.
- 3. Surgery after telecobalt therapy in carcinoma of the laryngopharynx is difficult. This must be kept in mind when designing a preoperative irradiation program. The dose in curable lesions should not exceed 3,000 r, with a weekly dose of 1,000 r.
- 4. Radiosensitivity of laryngopharynx cancers varies greatly from one patient to another. However, the best chance of cure is afforded by doses between 6,500 and 7,500 r.

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#### RADIATION THERAPY OF CARCINOMA OF THE TONSILLAR REGION\*

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THE purpose of this study is to report the results of radiation therapy at the Alice Crocker Lloyd Radiation Therapy Center of the University of Michigan of squamous cell carcinomas arising in the tonsillar region. Radiation therapy was completed on 102 patients with this diagnosis from the years 1955 through 1963. They constitute the material included in this report. We have eliminated lymphomas, soft tissue sarcomas and neoplasms originating from minor salivary glands; these tumors having a different natural history, radiosensitivity and prognosis than those of the squamous cell carcinomas.

An additional 9 patients were treated for recurrences; they had definitive prior treatment elsewhere with recurrence of the carcinoma. Three patients did not complete the prescribed course of radiation therapy and died of the disease before 5 years. These 12 patients have been eliminated from statistical consideration.

AGE AND SEX

The age distribution is shown in Table 1.

Table I
squamous cell carcinoma, tonsillar region
(1955 through 1963)

Age (yr.)	No. of Patients	Per Cent
30-39	3	2.9
40-49	16	15.7
50-59	37	36.3
60–69	31	30.4
70-79	13	12.7
80-89	2	2.0
	•	
Total	102	100.0

TABLE II

SQUAMOUS CELL CARCINOMA, TONSILLAR REGION
(1955 through 1963)

Histologic Diagnosis

	No. of Patients	Per Cent
Squamous cell carcinoma	96	94.1
Undifferentiated carcinoma	ı	1.0
Lymphoepithelioma	5	4.9
Total	102	100.0

The highest incidence of squamous cell carcinoma of the tonsillar region was found between the ages 50 through 69 years (68 patients or 67 per cent of the total number of patients). It is of interest to note that 3 patients were in the 30–39 year old group. Eighty patients were males and 22 females; a ratio of 4:1.

#### HISTOLOGY

Table II shows the distribution of cases according to the histologic classification. We have included in this study only the squamous cell carcinomas arising in the tonsillar region and have considered lymphoepitheliomas as a type of squamous cell carcinoma. Of 96 patients having a diagnosis of squamous cell carcinoma, 32 were alive without disease at 5 years (33.3 per cent). One patient was alive with recurrent neoplasm at 5 years, 12 died an intercurrent death and 51 died of the disease; a determinate 5 year survival of 39.3 per cent.

The 1 patient with a diagnosis of undifferentiated carcinoma died of the disease before 5 years. Of 5 patients with lymphoepithelioma, 2 were alive at 5 years, 2 died

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<sup>\*</sup> Presented at the Fifty-second Annual Meeting of the American Radium Society, Coronado Island, San Diego, California, March

Table III
squamous cell carcinoma, tonsillar region
(1955 through 1963)

	No. of Patients						
	T <sub>1</sub>	T <sub>t</sub>	T <sub>3</sub>	T <sub>4</sub>	Total	Per Cent	
Retromolar region	0	7	I	2	10	9.8	
Anterior tonsillar pillar	3	1 <b>6</b>	6	0	25	24.5	
Tonsillar fossa	5	14	7	0	26	25.5	
Posterior tonsillar pillar	2	4	ó	0	6	5.9	
Glossopalatine sulcus with major		•				,	
invasion of the tonsillar region	0	6	2	1	q	8.8	
Tonsillar region, unspecified	0	0	15	11	26	25.5	
Total	10	47	31	14	102	100.0	

an intercurrent death and only I patient died of the disease.

#### CLASSIFICATION

For this study we have adopted the following TNM classifications.

#### Ί

- T<sub>1</sub> Limited to one structure (retromolar region, anterior pillar, tonsillar fossa, posterior pillar).
- T<sub>2</sub> Tumor arising in one of the tonsillar structures with minimal to modest invasion of adjacent structure(s) plus the following regions: buccal mucosa, alveolar mucosa, palate, glossopalatine sulcus, tongue.
- T. Considerable invasion of adjacent structures.
- T<sub>4</sub> Massive involvement including definite bone destruction (primary site probably is not determinable and therefore is classified as carcinoma of the tonsillar region).

#### N

- No palpable lymphadenopathy.
- N<sub>1</sub> Homolateral lymphadenopathy, mobile.
- N<sub>2</sub> Bilateral or contralateral lymphadenopathy, mobile.
- N<sub>s</sub> Homolateral or bilateral lymphadenopathy, fixed.

#### M

- M<sub>0</sub> Distant metastasis not present beyond the neck.
- M<sub>1</sub> Distant metastasis present beyond the neck (i.e., lung, bone, etc.).

Whenever there was difficulty in allocating a tumor to a particular T, N or M group, we elected to classify the case in a less advanced group. The TNM classification was made on the basis of the findings on initial examination and was not changed afterward regardless of the subsequent course of events.

#### SITE OF ORIGIN

In addition to classifying the cases according to the above TNM classification, an attempt was also made to classify them according to the anatomic site of origin of the neoplasm in the tonsillar region (Table III).

Of the 10 patients whose lesions arose in the retromolar region, there were 3 alive at 5 years, 2 died of intercurrent disease prior to that interval and 5 died of the disease. This absolute 5 year survival of 30 per cent contrasts with the 12 patients alive without disease out of 25 with tumors of the anterior tonsillar pillar (48 per cent). In this group there was 1 patient alive with disease at 5 years while 1 had died of intercurrent disease. The remaining 11 patients had

died of the disease. Lesions of the retromolar region appear to have a worse prognosis, at least in this small number of cases. This may be due to the readiness of these lesions to involve the buccal mucosa, ascending ramus of the mandible and pterygomandibular fossa with the production of trismus, a poor prognostic sign.

Patients with carcinoma of the tonsillar fossa numbered 26. In this group there were 11 alive at 5 years (1 of whom had surgery for local recurrence), 5 died an intercurrent death and 10 died of the disease. Only 6 carcinomas originated in the posterior tonsillar pillars with 3 patients alive at 5 years and 2 having died an intercurrent death. Only 1 died of the disease.

Tumors involving the glossopalatine sulcus, tonsillar region and base of the tongue and which appear to have originated in the sulcus pose a difficult problem in their classification. We follow the Fletcher and Lindberg<sup>2</sup> classification of assigning them either to the tonsillar region or base of the tongue, depending upon which structure is most involved. Thus in our cases the lesions so classified had involvement of the tongue but with major invasion of the tonsillar structures. Cases that showed major involvement of the base of the tongue were classified in the oropharynx under that organ. In this group of 9 patients, 3 were alive at 5 years, 2 had died an intercurrent death and 4 died of the disease.

In 26 patients it was not possible to determine the site of the original neoplasm with any degree of certainty because the tumor extended to multiple structures in the tonsillar region. There were no patients allocated to the T<sub>1</sub> or T<sub>2</sub> groups. There were 15 patients with T<sub>3</sub> lesions, only 2 of whom were alive at 5 years, I died an intercurrent death and 12 have died of the disease. Eleven patients were classified as T<sub>4</sub>; I died an intercurrent death and the others died of the disease.

#### RESULTS

In Tables IV and V is shown the 5 year survival of patients according to the TNM

classification. It is of interest to note that of the 30 T<sub>1</sub> and T<sub>2</sub> cases without neck metastasis on initial examination, 17 were alive at 5 years without evidence of recurrence while 7 patients have died an intercurrent death, an absolute 5 year survival of 56.7 per cent, determinate 73.9 per cent. When we consider the 57 patients that constitute groups T<sub>1</sub> and T<sub>2</sub>, an absolute 5 year survival of 45.6 per cent is obtained. Included among the dead are I patient who was alive at 5 years but with disease present, I patient with pulmonary metastasis on initial visit and I patient who had local recurrence after irradiation but was later cured by subsequent surgery. The determinate 5 year survival is 57.4 per cent.

It is evident that as the primary lesion increased in size, the prognosis decreased (Table v). The same is true when the lymphadenopathy in the neck was advanced, as in the N<sub>2</sub>, N<sub>3</sub> groups where of 22 patients only 4 were alive at 5 years. Two had control of primary and metastatic lymphadenopathy after radiation therapy while 2 had control of the primary lesion but not of the neck metastasis. They had radical neck dissections with metastatic carcinoma found in the surgical specimens.

Of the 102 cases, 54 had palpable metastatic lymphadenopathy at the time of initial examination (52.9 per cent). In 48 cases the neck was thought to be free of metastatic disease (47.1 per cent).

The over-all absolute 5 year survival was 32.4 per cent, counting as if dead of the disease I patient who was alive with disease at 5 years and I who had recurrence of the primary lesion later cured by surgery (electrocoagulation of recurrence at primary site followed by radical neck dissection—patient alive at 13 years, 8 months after initial treatment). The determinate 5 year survival was 39.8 per cent.

### CONTROL OF PRIMARY LESION AND LYMPHADENOPATHY

Another manner in which to measure the effectiveness of radiation therapy upon the tumor is the determination of the rate of

Table IV squamous cell carcinoma, tonsillar region (1955 through 1963)

Tumor Size and 5 Year Survival

	No. of Cases		N <sub>0</sub>		N <sub>1</sub>		N <sub>2</sub>		N <sub>3</sub>	
$T_1$	10 (Alive Dead	7*) 3†)	5 (Alive Dead	3)	5 (Alive Dead	4*) 1†)	0		0	
Т,	47 Alive Al ē d.i. Dead	20) 1 10 16)	25 (Alive d.i. Dead	14) 7 4)	13 Alive Al ë d.i. Dead	3) 1 1 8)	1 (d.i.	1)	8 (Alive d.i. Dead	3) 1
T <sub>3</sub>	31 (Alive d.i. Dead	7 2 22	12 Alive d.i. Dead	4) 2) 6)	11 (Alive Dead	2 9	o		8 (Alive Bead	1) 7)
T <sub>4</sub>	14 (d.i. Dead	2) 12)	6 (d.i. Dead	2) 4)	3 (Dead	3)	1 (Dead	1)	4 (Dead	4)
Total	102 Alive Al ē d.i. Dead	34*) I I4 53†)	48 Alive d.i. Dead	21 11 16)	32 Alive Al č d.i. Dead	9*) I I 21†)	2 (d.i. Dead	1)	20 Alive d i. Dead	4) 1   15

<sup>\*</sup> One patient alive after surgery for postirradiation recurrence.

control of the primary lesion or of the metastatic spread in the neck when it was present initially. Of the 102 patients, 60

TABLE V
SQUAMOUS CELL CARCINOMA, TONSILLAR REGION
(1955 through 1963)
Tumor Size and 5 Year Survival

	No. of	5 Year	Survival
	Patients	Absolute	Determinate
		(per cent)	(per cent)
$T_1$	IQ	60.0*	70.0
$T_2$	47	42.6†	56.8
$T_{\mathbf{z}}$	31	22.6	24.1
$T_4$	14	0	0
		*****	
	102	32·4*†	39.8

<sup>\*</sup> One patient alive at 5 years after surgery for recurrence, considered dead of the disease at 5 years.

had permanent control of the primary lesion after radiation therapy (58.8 per cent) (Table vI); 32 had no control of the primary lesion (31.4 per cent); while in 10 it was not known if the primary lesion was controlled or not. By control of the primary lesion we mean that the patient had no evidence of recurrent neoplasm at the primary site, either at the end of the 5 year interval if the patient was alive, or if at the time of death the patient had no evidence of recurrent neoplasm, provided that the time of death was more than I year after the end of irradiation. If the patient died prior to I year after the initiation of radiation therapy, with the primary lesion considered controlled, the patient was nevertheless classified with the unknowns. The same criterion was used for the determination of the postirradiation status of the neck lymphadenopathy.

When the relationship existing between

<sup>†</sup> One patient had pulmonary metastasis before initial treatment.

Al c= Alive with disease at 5 years.

d.i. = Death intercurrent before 5 years.

<sup>†</sup> One patient alive at 5 years with disease, considered dead of the disease at 5 years.

the control of the primary lesion to its size (Table VII) is considered, it was found that 77.2 per cent of the 57 T<sub>1</sub> and T<sub>2</sub> cases had control of their primary lesions with radiation therapy; as the size of the primary increased, this control was less frequent. In the T<sub>2</sub> group it was found that 38.7 per cent, while in the T<sub>4</sub> cases only 28.6 per cent, had control of the primary lesion, although in this latter group there was no patient alive at 5 years, attesting to the aggressiveness of these large neoplasms.

In 54 patients there were metastases in the neck on the initial visit, and the lymphadenopathy was included within the fields of irradiation (Table VIII). In 14 patients this lymphadenopathy was controlled (25.9 per cent); it was not controlled in 31 (57.4 per cent) and it was not known whether control was obtained in 9 patients. Thirteen patients had permanent control of the primary lesion and metastatic disease after irradiation (24 per cent of the patients who had neck lymphadenopathy on initial examination).

It is important to note that not every patient who had primary control of the primary lesion survived 5 years. Of the 60 patients whose primary tumor was controlled by irradiation there were 32 alive at 5 years (53.3 per cent), 14 had died an intercurrent death (23.3 per cent) and 14 died from spread of the disease (23.3 per cent). Of the 32 whose primary lesion was not controlled by irradiation, I was alive at 5 years (salvaged by subsequent surgery), I was alive with disease at 5 years and 30 had died of the disease (93.8 per cent). Of the 10 patients in whom the status of the primary lesion was unknown, only I was known to be alive at 5 years (he did not have subsequent surgery) and 9 were dead of the disease.

Of the 14 patients who had control of the metastatic lymphadenopathy initially present in the neck, 9 were alive at 5 years (64.3 per cent); 2 of these had had radical surgery on the neck because of the appearance of metastatic lymph nodes below the area previously irradiated. Examination of

TABLE VI
SQUAMOUS CELL CARCINOMA, TONSILLAR REGION
(1955 through 1963)
Status of the Primary Tumor
After Radiation Therapy

	No. of Patients	Per Cent
Controlled	60	58.8
Not controlled	32	31.4
Unknown	10	9.8
Total	102	100.0

the surgical specimen revealed no metastatic lymph nodes in the irradiated areas. In the same group I patient was alive at 5 years with neoplasm, 3 had died an intercurrent death and I died of the disease. Of the 31 whose lymphadenopathy was not controlled by irradiation, 3 were alive at 5 years (9.7 per cent); all 3 had radical surgery for the treatment of the neck metastases. The other 28 patients all died of the disease at 5 years, 11 having had radical neck surgery in an unsuccessful attempt to control the disease. Of the 9 in whom the control of the metastases is not known. only I was alive at 5 years, the others having died of the disease.

Trismus before treatment was identified in 8 patients; 7 were dead of the disease at 5 years while 1 died an intercurrent death prior to that time. Five were classified as T<sub>4</sub>, while 3 were T<sub>3</sub>. Mandibular bone involvement was noticed in 6 patients, none of whom were alive at 5 years. One patient died an intercurrent death.

#### METHOD OF TREATMENT

Supervoltage radiation (Co<sup>60</sup>) became available to us in 1955. In the initial stages of the development of supervoltage techniques for the treatment of carcinomas of the tonsillar region, we relied on the use of a single lateral field on the same side as the primary tumor, occasionally supplemented by the use of an opposing lateral field but giving a smaller incident dose to it. A few

Table VII
squamous cell carcinoma, tonsillar region
(1955 through 1963)

Status of Primary Lesion After Irradiation, and Tumor Size

	No. of Patients	Controlled		Not Controlled		Unknown	
		No.	Per Cent	No.	Per Cent	No.	Per Cent
$T_1$	IO	8	80	2	20		
$T_2$	<b>4</b> 7	36	76.6	7	14.9	4	8.5
$T_3$	31	12	38.7	14	45.2	5	16.1
$T_4$	14	4	28.6	9	64.3	I	7.1
				**************************************		******	
Total	102	60	58.8	32	31.4	10	9.8

cases were treated using a rotational technique. Initially we delivered a tumor dose of approximately 6,000 r in about 6 weeks. As the technique of treatment evolved, we began to employ opposing lateral fields that crossfired the primary lesion and metastatic neck lymphadenopathy if present. Each field received the same incident dose while the total tumor dose to the primary site was increased to a total of 6,500 r and occasionally up to 7,000 r given over a period of 6 to 7 weeks.

The size of the fields of treatment varied depending upon the presence or absence of neck metastases. If no neck metastases were present, a field generally measuring 10×8 cm. was employed. We included within the volume irradiated the primary site plus the mid and upper cervical regions, the potential site for the develop-

TABLE VIII

SQUAMOUS CELL CARCINOMA, TONSILLAR REGION
(1955 through 1963)

Status of the Neck Lymphadenopathy After
Radiation Therapy

	No. of Patients	Per Cent
Controlled	14	25.9
Not controlled	31	
Unknown	9	57·4 16.7
m 1	<del></del>	***************************************
Total	54	100.0

ment of metastases. If metastases were present on initial examination, the primary and metastatic lesions were included whenever possible within the confines of the lateral opposing fields. However, if the metastatic lymphadenopathy in the neck was extensive, lower anterior cervical fields were added below the lower end of the lateral fields. An incident dose of 6,000-6,500 r was given to each of the lower anterior cervical fields over 6 to 7 weeks.

#### COMPLICATIONS

There were 2 patients who developed radionecrosis of the mandible. In 1 patient it was quite severe and was probably the cause of death, although for the purposes of the study he was considered as dying of neoplasm. In this patient the treatment was given using mainly a single field on the same side of the primary tumor.

The second patient had progressive dental caries after radiation therapy. Teeth were removed from the mandible, and areas of bone exposures developed in both sides of the body of the jaw. They subsequently healed after elimination of bone sequestrum.

It is practically universal for patients to develop dryness of the mouth, which ordinarily appears 2 to 3 weeks after initiation of radiation therapy. This is due to the effect of irradiation upon the parotid glands, unavoidably included in the field of tissue irradiated. This dryness of the mouth improves after several months post-

irradiation to the point where it is not bothersome, except when eating very dry foods. However, in a few cases, dryness of the mouth remains severe and does not appear to improve with time. The loss and alteration of taste—metallic taste—that patients experience early in the course of radiation therapy is also due to the decreased salivary secretion. It generally improves several weeks after the end of treatment.

Induration of the subcutaneous tissues of the areas irradiated was more frequent and pronounced when the treatment was given using mainly I field on the same side of the lesion. The degree of induration has been minimized since we have been using 2 opposing lateral fields that receive the same incident dose.

Some patients developed submental edema, which probably depends upon the extension of the fields of irradiation anteriorly onto the submental region. This edema is most likely due to the higher dose received by the tissues of the submental region and anterior neck, since this is a thinner portion than the area where the tonsillar region lies.

Of greater importance are the problems associated with teeth. Initially, patients who had teeth prior to irradiation had removal of all the teeth, alveolectomy and suture of the mucosa. Irradiation was started after the gum was well healed. In a few patients who had extensive lesions this policy was not carried out because of the poor prognosis and the time elapsed from extraction of teeth to initiation of irradiation.

Fifty patients were edentulous when treatment was initiated. Dental extractions in preparation for irradiation were carried out in 22 patients, while in 28 patients the teeth were present at the time of irradiation. In this latter group 8 patients had dental extractions following irradiation, in 1 of them there was an episode of radiation necrosis of the jaw which healed spontaneously after bone sequestra were eliminated.

Recently a significant change has been

made in the management of the teeth of patients who are to receive radiation therapy for oral neoplasms.3 The condition of the dentition is evaluated by our Dental Service: only those in poor condition are extracted and radiation therapy begins after the alveolar wound is healed. Residual teeth were subjected to a specific dental hygiene program consisting of brushing, oral lavage and flouride applications. After the end of radiation therapy the patients are also followed closely by the Dental Service. If dental caries develop they are immediately repaired before there is advanced decay of teeth. In this way extraction of teeth in the postirradiation period is avoided. None of the patients included in this study fell into this new dental program. Only time will tell if this dental program will prove superior to the routine extraction of teeth in lessening complications and increasing the patient's comfort by preserving the teeth.

#### DISCUSSION

Radiation therapy is effective in the curing of small and moderate sized primary carcinomas of the tonsillar region (T<sub>1</sub> and T<sub>2</sub> lesions). In Table VII we note that 80 per cent of the T<sub>1</sub> lesions were controlled by radiation therapy, while 76.6 per cent of the 47 T<sub>2</sub> lesion cases were also controlled by the same method. As the lesion increased in size, the rate of control decreased as expected. In the 31 T<sub>2</sub> cases it was 38.7 per cent and in the T<sub>4</sub> group 28.6 per cent.

The good results in the control of the primary neoplasm are not the only advantages of radiation therapy. It also avoids the mutilation and subsequent functional impairment that follows radical surgery to the primary site.

When lymph nodes are present in the neck, the prognosis becomes worse (Table IV). In the 48 patients who had no lymph node disease in the neck on initial visit, the absolute 5 year survival was 43.8 per cent, determinate 56.8 per cent. When lymph node disease was present in the neck,

the prognosis was poorer; absolute 5 year survival 22.2 per cent, determinate 27.5 per cent.

The control of metastatic lymphadenopathy by irradiation was not accomplished as frequently as control of the primary lesion. In 25.9 per cent, control of the lymphadenopathy was obtained by radiation therapy. This contrasts unfavorably with the 58.8 per cent of primary lesions controlled by radiation therapy.

The biologic aggressiveness of the tumor plays a major role in the cure of this neoplasm. This point can be appreciated by analyzing Table IX, where the salient de-

velopments of the clinical evolution of the 19 T<sub>1</sub> and T<sub>2</sub> patients who died of the disease are shown. Here it is shown that 7 patients (36.8 per cent) had their primary lesion controlled, but nevertheless died of the disease; 10 patients had no control of the neck lymphadenopathy after irradiation. Seven of these had radical surgery for the treatment of the recurrence at the primary site and/or of the metastases to the neck. In 1 patient there was recurrence in the neck after surgery. The others developed distant metastases after surgery without evidence of recurrence in the neck. In these 6 patients the efforts at curing the

Table IX

squamous cell carcinoma, tonsillar region

(1955 through 1963)

Analysis of Patients Recorded as Dead of the Disease (T1 and T2 Cases)

	Status of Status Primary Lesion Metast		Clinical Data	Death		
1. T <sub>1</sub> N <sub>0</sub> M <sub>0</sub>	Con.		Had also primary lesion in esophagus, base of			
2. T <sub>1</sub> N <sub>0</sub> M <sub>0</sub>	Not Con.		Recurred same place (anterior tonsil). No surgery	2 yr. 2 yr.	1 mo.	
3. T <sub>1</sub> N <sub>1</sub> M <sub>1</sub>	Probably Con.	?	Pulmonary metastasis	2 y 1 .	7 mo.	
4. T <sub>2</sub> N <sub>0</sub> M <sub>0</sub>	Con.	•	Pulmonary metastasis		io mo.	
5. T <sub>2</sub> N <sub>0</sub> M <sub>0</sub>	Not Con.		Recurred same primary site; neck metastases. No surgery		4 mo.	
6. T <sub>2</sub> N <sub>0</sub> M <sub>0</sub>	ş		Had another primary lesion at base of tongue	ı yr.	2 mo.	
	Not Con.		Recurred same place (fossa). No surgery	ı yr.		
	Con.	Not Con.	Developed carcinoma of esophagus after ra- diation therapy. No surgery	·	r ma	
9. T <sub>2</sub> N <sub>1</sub> M <sub>0</sub>	Con.	Not Con.	Had surgery for neck metastasis, recurred in	ı yr.	5 mo.	
77. N. N.	•	•	neck	•	7 mo.	
10. T <sub>2</sub> N <sub>1</sub> M <sub>0</sub>	}?		No follow-up or surgery	ı yr.	io mo.	
11. T <sub>2</sub> N <sub>1</sub> M <sub>0</sub>	Not Con.	Not Con.	Radical surgery to neck and primary lesion, recurred	2 VF	۲ mo.	
12. T <sub>1</sub> N <sub>1</sub> M <sub>0</sub>	Con.	Not Con.	Disseminated metastases (subcutaneous, chest wall, neck)	ı yr.	ı mo.	
13. T2 N1 M0	Not Con.	Not Con.	Radical surgery; disseminated metastases skin	*	II mo.	
14. T <sub>2</sub> N <sub>1</sub> M <sub>0</sub>	Con.	Not Con.	Radical surgery neck; distant metastases	2 yr.	3 mo.	
15. T <sub>2</sub> N <sub>1</sub> M <sub>0</sub>	Con.	Not Con.	Radical surgery neck; lung metastases	3 yr.	7 mo.	
16. T <sub>2</sub> N <sub>3</sub> M <sub>0</sub>	?	?	Severe necrosis jaw with trismus		8 mo.	
17. T <sub>2</sub> N <sub>3</sub> M <sub>0</sub>	;	Not Con.	Radical surgery to neck; disseminated metas-	·		
18. T <sub>2</sub> N <sub>3</sub> M <sub>0</sub>	Not Con.	Not Con.	No surgery	2 yr.	I mo.	
19. T <sub>2</sub> N <sub>3</sub> M <sub>0</sub>	Not Con.	Not Con.	Radical surgery; primary site and neck	ı yr.		

disease were doomed to failure in view of the biologic aggressiveness of the tumor.

In this respect it is somewhat disappointing to see that distant metastases have defeated a concerted effort by radiation therapy and surgery to control the primary lesion and regional spread of the disease.

Fletcher and Lindberg<sup>2</sup> reported on 104 patients with carcinomas of the anterior tonsillar pillar, retromolar trigone and tonsillar fossa. Their 5 year absolute survival was 36.5 per cent. This is statistically similar to our results (absolute survival 32.4 per cent in 102 patients). They concluded that the management of the primary lesion is essentially radiotherapeutic with surgical resection kept in mind for specific indications. We agree with this concept.

Recently, however, there has been a resurgence in the surgical treatment of carcinomas of the tonsillar region. Calamel and Hoffmeister<sup>1</sup> have presented data regarding the treatment of carcinoma of the tonsillar region by surgery, radiation therapy or a combination of both. Their 5 year determinate survival was 8.8 per cent in 57 patients who received radiation therapy alone. This is a low survival with radiation therapy, particularly when compared to our own series (39.8 per cent determinate 5 year survival) or that of others.<sup>2,4</sup> In the same study they reported 16 patients who were treated surgically. Nine were alive at 5 years for a determinate survival of 56 per cent, concluding that the cure rate results from surgery were evidently superior to that of radiation therapy, particularly in the most advanced cases. However it is worthy to note that 98 patients of the 122 were finally selected as fulfilling the requirement of their study; 19 being excluded because of treatment elsewhere or deficiency of follow-up information. Three patients who died postoperatively and 2 who had radiation therapy and died within I year were also eliminated from the study. They consider as cured patients who did not subsequently develop recurrent cancer, whatever the cause of death. Consequently, only 82 patients were considered for their

determinate 5 year survival rates.

It is difficult to compare this small surgical series with our material in view of the difference in TNM classification and the lack of knowledge regarding the presence or absence of initial metastatic lymphadenopathy in the neck in the surgical series. However, a larger series of surgically treated patients reported by Terz and Farr<sup>5</sup> give a 5 year relative survival of 26.5 per cent in 164 patients having radical surgery as treatment of the primary tumor. This survival is less than that obtained in the present study (determinate 5 year survival 39.8 per cent).

Our findings lend support to radiation therapy as the initial form of treatment of carcinoma of the tonsillar region, reserving surgery of the primary site only to cases with recurrence. If metastatic lymphaden-opathy is present in the neck it should be included in the fields of irradiation. However, if it cannot be controlled, radical surgery to the neck is indicated, provided of course that control of the primary lesion has been obtained and no distant metastases are present. The treatment of neck metastasis developing after irradiation is surgical.

#### SUMMARY

One hundred and two patients with a diagnosis of squamous cell carcinoma of the tonsillar region received complete Co<sup>60</sup> radiation treatment at the Alice Crocker Lloyd Radiation Therapy Center of the University of Michigan from the years 1955 through 1963. The absolute 5 year survival was 32.4 per cent, counting as if dead of the disease 1 patient who was alive with disease at 5 years and 1 who had recurrence of the primary lesion later cured by surgery. The determinate 5 year survival was 39.8 per cent.

The prognosis decreased as the primary lesion became larger or if there was regional metastasis. The degree of control of the primary lesion by irradiation was high in the T<sub>1</sub> and T<sub>2</sub> cases (80 per cent and 76.6 per cent, respectively). In larger lesions the

local control decreased. The neck lymphadenopathy was less amenable to control by irradiation than the primary lesion; only one-fourth of the patients with initial lymphadenopathy were controlled with radiation therapy.

The findings in this study lend support to the use of radiation therapy as the initial form of treatment of carcinoma of the tonsillar region.

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# CERVICAL LYMPH NODE METASTASES FROM CARCINOMA OF UNDETERMINED ORIGIN\*

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THE presence of an enlarged lymph node in the cervical region should always be a cause of concern to the patient and to the physician. A metastatic lymph node in the neck arising from a carcinoma of undetermined origin presents a special problem of careful diagnosis, evaluation, and treatment. It is in this instance where the otorhinolaryngologist should play an important role because of his knowledge of the regional anatomy and pathology of the head and neck.

Many articles have been published about metastatic lymph nodes in the neck but few of them have been devoted to the problem of metastatic cervical lymph nodes from an occult primary lesion.<sup>1,4,7,10,16,21</sup>

In this article we shall review the literature on this subject, report our experience with these lesions, and discuss the problems encountered with the diagnosis and treatment.

#### MATERIAL

From 1939 to 1967, a group of 80 patients who initially presented themselves with a mass in the neck without evidence of a primary lesion was seen at the I. González Martinez Hospital and they constitute the basis of this study.

Cases referred to our institution with the diagnosis of metastatic carcinoma from an unknown primary lesion, and in whom the site of origin was discovered after a careful examination, or during treatment, were excluded from the study.

#### AGE AND SEX DISTRIBUTION

Table I shows the distribution by age and sex. Eighty per cent of the cases were over

50 years of age at the time of diagnosis. The youngest patient was 21 years old, and the oldest 105 years old. The median age for this group was 62 years.

Fifty-five of the patients were males (69 per cent) and 25 cases were females (31 per cent), a male to female ratio of 2.2:1.

#### SYMPTOMS

The most frequent complaint in our cases was an enlargement or swelling of the neck, sometimes accompanied by throat discomfort, earache, weight loss and other general symptoms.

Only I case in our series was asymtomatic and an enlarged supraclavicular lymph node was found on a routine examination.

Twenty-eight patients (35 per cent) noticed the presence of an enlarged lymph node in the neck from 1 to 2 months prior to diagnosis. Seventy-eight per cent of the patients had symptoms from 1 to 6 months before a definite diagnosis of metastatic

TABLE I

AGE AND SEX DISTRIBUTION

Age Group	Male	Female	Total	Per Cent
(yr.)				
20-29	1		I	r
30-39	3	3	6	8
40-49	6	3	9	11
50-59	17	3	20	25
60-69	12	5	17	21
70-79	8	6	14	17
80-89	6	3	9	11
90	2	2	4	5
_				
	55	25	80	100

<sup>\*</sup> Presented at the Fifty-second Annual Meeting of the American Radium Society, Coronado Island, San Diego, California, March 1-5, 1970.

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disease was made. The average duration of symptoms was 3 months.

Table II shows the distribution of the cases in relation to the duration of symptoms.

# NUMBER AND LOCATION OF LYMPHADENOPATHIES

In our series the most common finding was a group of matted lymph nodes giving the appearance of a large tumor mass in the neck, present in 63 of our patients. Seven patients had a single enlarged lymph node and 10 patients had multiple enlarged lymph nodes.

Table III shows the distribution of cases in relation to the number and location of

the lymphadenopathies.

The metastatic manifestation was present in the right side of the neck in 33 cases (41 per cent), in the left side in 34 cases (43 per cent), and was bilateral in only 13 cases (16 per cent). Most of the metastases were found to be fixed to the deep structures, and this occurred in 53 cases (66 per cent). The lymph nodes were found to be movable only in 20 cases, and in 7 cases the mobility of the lymph node was not stated on the record by the examiner. The size of the metastatic lymph nodes ranged from 0.5 to 18 cm. in diameter, with an average of 7 cm. In 4 cases the only finding was a scar in the neck, indicating the site of the excision biopsy previously performed by the referring physician.

#### DIAGNOSIS

Patients coming to our institution with a presenting sign of an enlarged lymph node in the cervical region, routinely have a complete history and physical examination. Special attention is directed to the head, neck, and upper gastrointestinal regions. The patients are specifically questioned as to previous surgical interventions, diagnosis and results of the same. The history also includes a thorough review of all systems. The patients are then evaluated by an otorhinolaryngologist who makes a thorough examination of the head and neck, includ-

Table II

DURATION OF SYMPTOMS

Duration in Months	No. of Cases	Per Cent
Asymptomatic	1	I
1-2	28	35
3-4	19	24
5-6	14	18
7-8	6	8
9–10	2	2
11-12	3	4
More than 12 mo.	3	4
Not stated	4	5
Total	80	100

ing the skin and scalp. The examination includes nasopharyngoscopy, indirect and direct laryngoscopy, and palpation of the entire tongue and floor of the mouth. Laboratory procedures are then obtained including routine blood studies, roentgenograms of the chest, skull, paranasal sinuses, and soft tissues of the neck, and, if indicated, upper gastrointestinal studies including the esophagus.

If the primary lesion is still not determined, urologic, gynecologic and proctologic evaluations are obtained. Bronchoscopy and esophagoscopy with collection of secretions and aspirations for cytologic studies are also performed, as well as multiple representative biopsies of different areas of the nasopharynx and base of the tongue.

Table III

NUMBER AND LOCATION OF LYMPHADENOPATHIES

	Single	Mul- tiple	Mass	Total
Upper neck	2	ı	18	21
Upper and mid neck		1	5	6
Middle neck	2	1	9	12
Lower neck	*******		Ī	1
Whole neck		2	15	17
Supraclavicular	2	3	15	20
Suprasternal Upper and	I			I
supraclavicular	******	2		2
-		-	********	
	7	10	63	80

Most of our cases are examined by 2 or more members of the Head and Neck Division in an effort to discover the primary lesion. The extent of the studies varies, depending on the site and characteristics of the presenting metastatic lesions. In high or upper jugular metastases, more importance is given to the nasopharynx, tonsils, and palate, while in supraclavicular metastases the search is directed to the thyroid, cervical esophagus, or organs of the chest and abdomen.

#### METHOD OF DIAGNOSIS

When these cases of suspected neck metastasis were seen without previous pathologic diagnosis, a biopsy of the lymph node was planned only after a thorough search failed to reveal a primary lesion. The choice of the method depended on the location, size and mobility of the lymph node, also taking into consideration the general condition of the patient.

In 40 cases (50 per cent), the diagnosis was made by lymph node incision. In 29 of the cases (36 per cent), a lymph node excision was made, and only in 6 cases (7 per cent), aspiration biopsy of one of the lymph nodes was done for diagnostic purposes. A radical neck dissection was performed in 2 cases, following a frozen section with a positive diagnosis of metastasis. In 3 cases of the series the method of diagnosis was not stated in the patient's chart.

Table IV shows the distribution of the material by method of diagnosis.

#### PATHOLOGIC DIAGNOSIS

Table v shows the distribution of our cases according to pathologic diagnosis. The most common type was epidermoid carcinoma, 42 of the cases in the series (52 per cent), followed by anaplastic carcinoma in 27 cases (34 per cent). The diagnosis of adenocarcinoma was made in 5 cases, and 6 other cases were diagnosed as carcinoma.

#### TREATMENT

Table VI illustrates the treatment modality of the metastatic manifestation of the

TABLE IV
METHOD OF DIAGNOSIS

	No. of Cases	Per Cent
Lymph node incision	40	50
Lymph node excision	29	36
Aspiration (needle)	6	8
Radical neck dissection	2	2
Not stated	3	4
Total	80	100

TABLE V

	No. of Cases	Per Cent
Epidermoid carcinoma	42	52
Adenocarcinoma	5	6
Anaplastic carcinoma	27	34
Carcinoma	6	8
Total	80	100

Table VI
TREATMENT OF METASTASES

	No. of Cases	Per Cent
Surgery		
Excision only	4	5
Excision plus		-
radiotherapy	13	16
Radical neck dissection	3	. 4
Radical neck dissection	_	•
plus radiotherapy	3	4
Radiotherapy	~	•
External, complete	24	30
External, incomplete	14	18
External and interstitia	1 4	5
Chemotherapy	ī	I
No treatment	14	18
	<u>.</u>	
Total	80	100

patients included in our series. Of the total of 80 patients, 14 were not treated (18 per cent). These included patients who were in such a poor condition that they were considered terminal cases; others had generalized metastases and treatment was not considered worthwhile. In some cases patients refused treatment.

The most frequent type of treatment used in our series was external radiotherapy (orthovoltage roentgen therapy and Co60 teletherapy since 1956). This modality was the primary treatment in 42 cases [52 per cent). The radiotherapy course was considered complete in 24 cases and incomplete in 14 cases. External irradiation, complemented by interstitial implantation of radioactive sources was performed in 4 cases. Surgery alone or surgery plus radiotherapy was the treatment of choice in 23 patients. In 4 cases (5 per cent) the only form of treatment was simply an excision of the lymph node. In 13 cases (16 per cent) the excision of the lymph node was followed by a course of radiotherapy. Radical neck dissection was performed in 6 of the cases; in 3 of them it was the only modality of treatment, and in the other 3 cases surgery was followed by external radiotherapy. One advanced case with multiple metastases was treated by chemotherapy. Surgery was performed only on a limited number of cases, because of the poor general condition of the patients, the advanced stage of the disease at the time of diagnosis, or because of specific medical contraindications to surgery.

#### RESULTS

Table VII shows the over-all survival. The 80 cases in our series are eligible for 1 year survival, and 32 (44 per cent) of the 73 cases traced are alive at the end of 1 year. The 3 year survival was 20 per cent and the 5 year survival 17 per cent.

Table VIII shows the survival of the treated cases. The I year survival in this group was 54 per cent. Eight patients remain alive (2I per cent) out of 38 traced and eligible for 5 year survival.

Table Ix shows the 3 and 5 year survival in relation to the treatment modality. Two out of 4 patients who had only excision of the metastatic lymph node survived 5 years or more, and also 2 out of 5 patients with excision of the lymph node plus radiotherapy remained alive at the end of 5 years. Two out of 3 patients who had

Table VII

OVER-ALL SURVIVAL

(Direct Method)

Years Sur- vived	No. of Cases Eligible	No. of Cases Traced	No. of Cases Surviving	Per Cent Sur- vival
I	80	73	32	44
2	70	68	19	28
3	61	60	12	20
4	54	53	9	17
5	49	48	8	17

TABLE VIII
SURVIVAL IN TREATED CASES
(Direct Method)

Years Sur- vived	No. of Cases Eligible	No. of Cases Traced	No. of Cases Surviving	Per Cent Sur- vival
I	66	59	32	54
2	56	54	19	35
3	47	54 46	12	26
4	42	<b>4</b> <sup>I</sup>	9	22
5	39	38	8	21

radical neck dissection survived 5 years, and none of the 2 with radical neck dissection followed by radiotherapy and eligible for 5 year survival remained alive. Only 2 of the patients who received radiotherapy as unique modality of treatment are alive at the end of 5 years. The patient with generalized metastases treated with chemotherapy died within 2 months of admission.

# ANALYSIS OF CASES WHERE THE PRIMARY LESION WAS FOUND

In our series the primary lesion was eventually found in 8 of the 80 cases and the time of discovery ranged from 3 months to 9 years after treatment of metastasis. Detailed analysis of these cases is shown in Table x.

In 5 cases the primary lesion was found above the clavicle and in 3 cases in organs below the clavicle. The most frequent site of the primary lesion above the clavicle was the base of the tongue, and below the clavicle the esophagus.

Table IX
3 and 5 year survival by treatment modality
(Direct Method)

	3 Year Survival	5 Year Survival
Surgery		
Excision only	3/4	2/4
Excision plus radiotherapy	4/7*	2/5*
Radical neck dissection	2/3	2/3
Radical neck dissection plus	, 0	, ,
radiotherapy	1/3	0/2
Radiotherapy	, 0	•
External, complete	1/17	1/15
External, incomplete	1/7	1/5
External and interstitial	0/4	0/3
Chemotherapy	0/1	0/1
No treatment	0/14	0/10
Total	12/60*	8/48*

<sup>\*</sup> Excluding I case lost to follow-up.

Radiotherapy was the treatment of choice for the primary lesion in 5 of the cases. One case with the primary tumor in the base of the tongue was treated by radium needle implantation only, the other patient with primary tumor in base of tongue was treated by interstitial radium implantation followed by surgery. The patient with carcinoma of the stomach was not treated.

#### DISCUSSION

The cervical region, because of its rich-

ness in lymphatic nodes and vessels, is the frequent site of metastases from different areas, near or distant. This vast network of lymphatic vessels and nodes drains the organs of the head and neck including the skin and scalp.<sup>12</sup> There is no barrier separating the lymph circulation of the neck from the infraclavicular areas; therefore, metastatic lymph nodes from primary lesions in the thoracic and abdominal organs are to be expected with greater or less frequency.<sup>14</sup>

Although the lymphatic drainage of each area in the head and neck is quite specific with respect to anatomic distribution, one must remember that there exist interconnections between the groups of lymph nodes. The frequency of metastases from different head and neck regions to specific groups or levels of cervical lymph nodes is usually predictable; however, individual differences may exist. The metastatic potential of primary lesions depends on the amount of lymphatic drainage, the type of malignancy, and other unknown factors, chemical or physical.<sup>2</sup>

Many primary lesions such as hypopharyngeal and pyriform sinus tumors frequently extend directly by continuity into the deep cervical region simulating deeply fixed metastases. Some authors believe that tissues or organs which are subjected to frequent or continuous pressure or movement such as the oropharynx, hypopharynx, soft palate, uvula, and tongue when in-

Primary Lesion	Age (yr.)	Sex	Location of Metastasis	Treatment of Metastasis		val to overy	Treatment of Primary Lesion	Status	Status and Surviva	
Base of tongue Base of tongue Base of tongue		M M M	Upper neck Upper neck Upper neck	Excision Excision Radiotherapy	9 yr. 3 yr. 1 yr.	8 mo. 6 mo. 5 mo.	Radiotherapy Radium implantation Implantation and	10 yr. 7 yr. 5 yr.	10 mo. 10 mo. 7 mo.	D NED NED
Esophagus Esophagus Soft palate Nasopharynx Stomach	76 81 68 39 79	F F M M	Suprasternal Supraclavicular Upper and mid neck Whole neck Upper, mid neck and supraclavicular	Excision Radiotherapy RND Radiotherapy Radiotherapy	ı yr.	3 mo. 4 mo. 5 mo. 5 mo. 8 mo.	surgery Radiotherapy Radiotherapy Radiotherapy Radiotherapy Nadiotherapy None	2 yr. 1 yr. 13 yr. 1 yr. 1 yr.	4 mo. 10 mo. 11 mo. 3 mo. 4 mo.	D AWD NED D D

<sup>\*</sup> Survival from treatment of metastasis.

RND=Radical Neck Dissection; D=Dead; NED=No Evidence of Disease; AWD=Alive With Disease.

vaded by tumors will lead to metastases more often than fixed tissues like the hard palate, gums, sinuses, and nasal cavity.18 Anaplastic or highly undifferentiated tumors usually spread rapidly to the lymphatics, as in nasopharyngeal and tonsillar cancers.

It is important to correlate the pattern of growth of certain lesions in this area with the relative frequency of metastases. Tumors of the lips, gums, soft and hard palate, paranasal sinuses, and intrinsic larynx metastasize late, while lesions of the nasopharynx, base of the tongue, hypopharynx, anterior surface of the epiglottis and tonsils metastasize early, and frequently in the form of multiple and bilateral metas-

Clinically a metastatic cervical lymph node suggests a very aggressive and malignant lesion. The lymph nodes are hard, movable or fixed to the deep structures of the cervical region with a history of rapid growth. They are frequently multiple in number, and coalesce into large masses. All lymph node enlargements, especially after the fifth decade of life, should be considered cancerous, unless proven otherwise.14

The management of metastatic lymph nodes from an unknown primary lesion is rather complex and one in which there is no complete agreement. The treatment of cervical metastatic lymph nodes, in general, consists fundamentally of 2 methods: surgery and irradiation.<sup>21</sup> Each case should be evaluated separately according to individual characteristics or conditions, as well as local and systemic factors.

Surgery is the usual treatment of choice for metastatic cervical lymph nodes.<sup>28</sup> A unilateral or bilateral neck dissection should be considered when indicated.17,18,20,29,32 The criteria for operability should first be met: patient should be in a satisfactory condition to withstand the procedure; and the lymph nodes in question should be resectable. Fixation to deep structures and involvement of lymph nodes in relatively skull, are frequent contraindications to the usual lymph node resection procedures. Distant metastases as well as the presence of an uncontrollable primary cancer also usually constitute contraindications to radical neck surgery. Instances which include cervical and or supraclavicular lymph node metastases from primary lesions in pulmonary or abdominal organs are also contraindications to neck dissection procedures.

Radiotherapy is frequently indicated for treatment of metastatic cervical lymph nodes.19,22 The efficacy of this modality of treatment as a preoperative adjunct to surgery in decreasing the incidence of local recurrences has been reported. Its usefulness as a postoperative treatment in cases in which it has not been possible to extirpate all of the neoplasm has also long been recognized. In addition, radiotherapy has also been of some effect in inoperable cases, with frequent significant local control.8,5,11,15

In the specific cases in which a pharyngeal primary lesion is highly probable (lymphoepithelioma or undifferentiated epidermoid carcinoma) in the upper or middle cervical lymph nodes, radical radiotherapy of the involved lymph nodes and including the pharynx has been of greatest benefit.

Prior to treatment, the histopathologic diagnosis should be established and the previously mentioned diagnostic studies should be exhausted.

Our experience with 80 cases of metastatic cervical lymph nodes in patients in whom the primary site was unknown, illustrates the many problems in diagnosis and treatment which these patients present. The most important factor in the management of these patients is to undertake a meticulous and thorough search for a possible primary lesion. Only after this is done, do we feel that definitive treatment is justified. However, treatment should not be delayed once the necessary investigation has been carried out, and one should not wait until the primary tumor is proven before treatment of the metastatic lymph inaccessible areas, such as the base of the "nodes. Patients under radiotherapy should be examined periodically, because areas of early radiation mucositis may indicate the site of the primary tumor, and biopsy should be taken to establish a definite diagnosis.

In our experience, the location of lymphadenopathy has been of some help in indicating the probable site of the primary lesion, and if the enlarged lymph node is initially in the mid or upper cervical chain, a pharyngeal primary tumor is likely, whereas an enlarged supraclavicular lymph node has usually indicated an infraclavicular primary lesion. This has also been the experience of other authors.<sup>6</sup>

In general, metastatic disease has a poor prognosis. This is complicated in cases in which only the metastatic manifestation is found and the primary tumor remains occult. However, this situation is not hopeless and there is a difference in prognosis depending upon the location, number and size of lymph nodes as well as the histopathologic diagnosis. Patients with metastatic lymph nodes in the upper and mid cervical region have a better prognosis than those with metastatic lymph nodes in the supraclavicular and low cervical regions. Metastases in the lower neck and supraclavicular fossa are usually due to primary tumors originating in organs below the diaphragm, while those in the upper levels arise from lesions in the head and neck; these may be arrested or controlled when included in the irradiation field at the time of treatment to the metastatic disease. All of the 8 five year survivors in our series had the metastatic manifestation in the upper levels of the neck. The importance of combined treatment when indicated should be pointed out as another factor which can influence the prognosis.

Careful continued follow-up of these patients is of utmost importance in order to discover the primary lesion at an early stage of tumor growth when effective treatment can be carried out.

#### SUMMARY

Our experience at the I. González Mar-

tinez Hospital with 80 cases of metastatic carcinoma to cervical lymph nodes from an undetermined primary tumor has been reviewed.

The majority of cases was found above the age of 50 years and the male to female ratio was approximately 2 to 1.

In 63 of the 80 cases studied, the metastatic manifestation constituted a large tumor mass, and due to this fact, lymph node incision or needle biopsy was performed for diagnostic purposes in most of the cases.

Epidermoid carcinoma and anaplastic carcinoma were the most frequent pathologic diagnoses, 52 and 34 per cent, respectively.

Radiotherapy was the treatment of choice in 52 per cent of the cases; most of the cases who underwent radiotherapy as primary treatment had advanced metastatic disease or were not considered candidates for radical surgery. Surgery was the main treatment modality in 23 of the cases (29 per cent), but 16 of them received additional post-operative radiotherapy. Fourteen cases received no treatment. The 5 year survival for the 38 treated cases traced was 21 per cent. The 8 cases who survived 5 years or more had their metastatic lymph nodes in the upper and mid parts of the neck.

The primary lesion was discovered in 8 of our 80 cases and these are analyzed separately.

In our opinion, early detection of an enlarged lymph node in the neck, careful search for the origin of the primary lesion, and the close collaboration between surgeons and radiotherapists in the evaluation and management of patients with metastatic disease from undetermined origin will lead to the best results. A meticulous follow-up in these patients is considered of utmost importance to discover the primary lesion at an early stage of tumor growth when effective curative treatment can be established.

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# HYDROXYUREA AND RADIATION THERAPY IN AD-VANCED NEOPLASMS OF THE HEAD AND NECK\*

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THE radiosensitizing properties of hydroxyurea have recently been documented in the literature.<sup>3-6</sup> This agent has been used by some investigators combined with radiation therapy and surgery in all stages of oral carcinoma.<sup>8-5</sup> When conventional doses of radiation therapy are combined with radical surgery and then a drug is added, it is difficult to ascertain which modality is the most effective agent. This is especially true in early cases where radiation therapy and surgery used, alone, each have a well established cure rate.

We decided to employ hydroxyurea in an intermittent dose schedule combined with conventional doses of radiation therapy in advanced lesions where the usual survival rates and regression rates are low. The use of hydroxyurea in early cases of malignancy seems to us to be superfluous. In advanced T 3 and T 4 lesions no one doubts that help is needed by surgeon and radiotherapist alike.

Following is a report of our results attained to date with hydroxyurea and radiation therapy combined to treat T 3 and T 4 oral lesions.

#### METHOD OF TREATMENT

Hydroxyurea was supplied by E. R. Squibb and Company as the dried powder in 0.5 gm. capsules. The drug was administered intermittently, 80 mg./kg. of body weight, given in a single oral dose every third day. Simultaneously, therapeutic radiation was given over a period of 4–10 weeks with conventional doses. In most instances hydroxyurea was administered during the time of radiation therapy, then discontinued. In several patients the drug was continued for 8–9 months post therapy.

Radiation therapy was administered in

all cases with cobalt 60, using a Picker C 8,000 rotational unit with a 2 cm. diameter source and 60-80 cm. skin-source distance.

#### CASE MATERIAL

In the period May 1968 through May 1969, 26 cases were treated. These included primary lesions as shown in Table 1.

The cases were staged according to the method of the American Joint Commission on staging of Cancer (Table II). Three of the cases were in Stage III and 23 cases in Stage IV. No cases in Stage I or II were treated in this series. These figures indicate the advanced nature of the cases treated.

The tumors were graded as shown in Table III.

#### RADIATION DOSES

In 5 cases no radiation therapy was administered concomitantly with the hydroxyurea. In all 5 of these cases radiation therapy had been previously administered and hydroxyurea was given because of recurrent tumor.

In 9 cases of the 21 treated with irradiation and hydroxyurea concurrently, radiation therapy was given previously in doses of 6,000-7,000 rads and combined treatment was then administered for recurrence. Two of these cases also had surgical treatment with their radiation therapy prior to combined hydroxyurea and radiation therapy for recurrence.

In 2 additional cases surgery had been used alone before combined hydroxyurea and radiation therapy for recurrent tumor.

Ten cases were treated with combined hydroxyurea and radiation therapy. No prior therapy was administered in these cases.

The radiation doses administered in con-

<sup>\*</sup> From the Department of Radiology, Mercy Catholic Medical Center, Philadelphia, Pennsylvania.

Table I

CASE MATERIAL

(May 1966 through May 1969)

Lesion	No. of Cases
Carcinoma of the tongue Carcinoma of the larynx Carcinoma of the tonsil Carcinoma of the pharynx Carcinoma of the floor of the mouth Carcinoma of the pyriform sinus Carcinoma of the buccal surfaces Carcinoma of the maxillary antrum Carcinoma of the gingiva	8 6 3 2 2 1 1
Carcinoma of the cervical esophagus	I 
Carcinoma of the pyriform sinus	_
	I I —

junction with hydroxyurea after recurrence or with no prior therapy varied from 2,000 rads in 2 weeks to 7,000 rads in 7 weeks as follows: no radiation, 5 cases; >4,000 rads, 4 cases; 4,000 rads, 4 cases; 5,000 rads, 12 cases; and <7,000 rads, 1 case.

The radiation cutaneous and mucosal reactions in general were of the order expected from the radiation dose alone and were not potentiated by this drug.

#### HYDROXYUREA DOSAGE AND EFFECTS

The dose of hydroxyurea (CH<sub>4</sub>N<sub>2</sub>O<sub>3</sub>) administered was 80 mg./kg. every third day except in 1 case where 20 mg./kg. was administered daily. This latter case and 3 cases in which total doses of only 3 and 6 gm. respectively were administered are excluded from the analysis of the drug effects below. In the 22 cases remaining,

total doses of 30 to 704 gm. in 12 to 428 days were administered during treatment.

In all but 2 cases hydroxyurea was discontinued shortly after the completion of radiation therapy, but in 2 patients the drug was continued as chronic therapy. In 1 of these patients 365 gm. of hydroxyurea has been given in 201 days and in the other, 704 gm. of hydroxyurea was given in 428 days. In the patients treated with chronic hydroxyurea administration the drug was tolerated without toxicity except for mild leukopenia. It seemed to us that the drug was safe to use at this dose level for chronic therapy.

As noted above the cutaneous and mucosal radiation reactions were not enhanced by hydroxyurea, even in cases with enhanced tumor effects and/or previous radiation therapy.

Complications of hydroxyurea therapy included hematologic, cutaneous, and general effects.

Anemia manifested by a hemoglobin drop of 2-3 gm. per cent developed in 5 cases including 1 case treated with hydroxyurea alone. In the other patients the anemia could not be attributed to the disease alone or to bleeding and it responded to administration of iron.

Leukopenia was common with levels of 2,000-3,500/cu. mm. noted in 12 of 22 patients treated with hydroxyurea more than 1 week, including 1 patient treated with 55 gm. of hydroxyurea alone. The white blood cell level generally rose to 3,000/cu. mm. with the omission of 1 or 2 doses of hydroxyurea and then the drug was continued.

TABLE II
THM CLASSIFICATION AND STAGING OF CASES

TNM	No. of Cases	TNM	No. of Cases	TNM	No. of Cases	Stage	No. of Cases
T 1 T 2 T 3 T 4	2 4 7 13	N o N 1 N 2 N 3	2 5 6 13	М	4	Stage I (T 1, N 0) Stage II (T 2, N 0) Stage III (T 1, T 2, T 3, N, M, T 3, N 0) Stage IV (N 2, N 3, M)	0 0 3 23

TABLE IIIA	
TNM CLASSIFICATION OF CAS	ES

	Тı	T 2	T-3	T 4	Νο	Nı	N 2	N 3	M
No. of patients Recurrent	2 2	4	7 6	13 4	2 I	5 3	6 3	13 9	4 3
Previously untreated Living and well	0	0	I	9	I	2	3	4	1
Living with disease Negative autopsy	-	0	I O	0	0	I	0	0	0

Three of the 22 patients developed white blood cell levels of 600, 600 and 1,400 cells/cu. mm., respectively, and in these cases hydroxyurea was discontinued completely. One of these patients had pancytopenia including a thrombocytopenia of 16,000/cu. mm.

One patient developed rhinorrhea and a generalized pruritic erythematous rash after each dose of hydroxyurea.

In 2 patients severe nausea necessitated discontinuance of hydroxyurea.

Cerebral infarcts developed in 2 patients. One patient died as a result of his infarct. He had 3 previous "strokes" over a period of 5 years, and had been known to have carotid artery stenosis demonstrated by carotid angiography 2 years prior to hydroxyurea therapy. At autopsy severe arteriosclerosis was present and no residual tumor was found. It is our feeling that the cerebral infarction was not related to his hydroxyurea therapy.

The second patient also had a previous

"stroke" and severe arteriosclerosis. He subsequently died of the effects of his neoplasm.

The effect of hydroxyurea on the tumor could not be judged in the 3 cases receiving too little of the drug. One of the 5 patients receiving hydroxyurea alone had an objective remission. In this patient a recurrent mass in the left neck completely disappeared during the course of hydroxyurea therapy but recurred in 6 weeks while the drug was being continued.

We felt that the radiation effect was enhanced in 13 of 18 patients treated with combined hydroxyurea and radiation therapy. This enhanced effect was noted in 5 of 8 recurrent cases and 8 of 10 primary cases. In the latter cases the tumor regressed more promptly and completely than we have anticipated from radiation therapy alone.

RESULTS

The results were evaluated according

TABLE IIIB
STAGING AND GRADING OF CASES

	Stage					Grade			
	I	II	III	IV	I	2	3	4	?
No. of patients Recurrent Previously	0	0	3 3	23 13	2 1	18 9	3 3	I	2 2
untreated			0	10	r	9	0	0	0
Living and well			0	5	0	5	0	0	0
Living with disease			0	I	0	1	0	0	0
Negative autopsy			1 '	I	0	ı	1	0	0

to the TNM classification, staging, grade of tumor and whether the tumor was primarily untreated or recurrent. The results seem to depend on the lack of previous treatment more than the other factors in the cases treated.

Sixteen recurrent tumors were treated with combined hydroxyurea and radiation therapy; 3 were in Stage III, and I3 in Stage IV. All of these died and in only I did autopsy show no evidence of tumor. The patients lived for I-6 months from the start of combined therapy with an average length of life of 3 months.

Ten previously untreated patients were treated with combined hydroxyurea and radiation therapy. All of these were in Stage IV. The average length of life of these patients from the start of therapy is currently 6.4 months. Three patients are living and well, 4–14 months from the beginning of therapy. One patient died 2 months after beginning therapy of a cerebrovascular accident and no tumor was found at autopsy. One patient died of intercurrent disease after 12 months and no tumor was found at autopsy.

Richards and Chambers<sup>5</sup> also noted a number of good results in their Stage III and IV patients. The difference between the treated and untreated patients, we believe, lies in the lessened oxygen tension secondary to scarring from previous treatment, producing a poor response to radiation therapy. This may also interfere with the effects of chemotherapy. Richards and Chambers<sup>5</sup> report an enhanced effect in metastatic tumor in lymph nodes. We were more impressed with the response of the local lesion than the lymph node metastases from the clinical standpoint.

All living patients had Grade 2 tumors. There were no patients in Stage 1 cr 11. All 3 patient's in Stage 111 died 3 months after beginning treatment. One of these patients died of a pulmonary embolus and no tumor was found at autopsy. Twenty-three patients were in Stage 1v. Three of these patients are living and well 4-14 months following the onset of therapy.

In 2 patients who died of cerebrovascular accidents 2 months and 13 months, respectively, after onset of therapy, no tumor was found at autopsy.

#### REPORT OF CASES

The following cases illustrate some of the patterns noted in this series of cases.

Case I. P.H. A 59 year old white man was first seen at Misericordia Division of the Mercy Catholic Medical Center on June, 1968 with a history of pain in the left ear and jaw for 2 months prior to admission. He saw a dentist and a physician without relief by simple measures and finally consulted a surgeon because of the development of a lump in the neck. A biopsy was performed of the lesion involving the tongue. This revealed a squamous cell carcinoma, Grade 2.

On examination there was a large lesion involving the left side of the soft palate, the tonsil, lateral pharyngeal wall, posterior two-thirds of the tongue on the left side and crossing the mid line to involve the right side of the base of the tongue and anteriorly to involve the left floor of the mouth. The over-all dimensions were  $5\times6\times5$  cm. There was a fixed lymph node in the left upper neck measuring  $6\times6\times4$  cm. A chest roentgenogram was negative. Liver scan showed a cold area in the inferior portion of the right lobe of the liver but a needle biopsy of the liver was negative. The lesion was staged T4, N4, Mo?

He was started on radiation therapy combined with hydroxyurea. Between June 20, 1968 and August 7, 1968 a dose of 7,000 rads was achieved in the left side of the tongue and pharynx employing parallel opposed fields using cobalt 60 irradiation. A dose of 900 rads additional was given to the residual mass in the left upper neck using conventional radiation therapy and on August 13, 1968 a single plane radium implant was applied to the left side of the neck delivering an additional 3,000 gamma roentgens to this lymph node.

A moderately severe mucositis developed in the mouth with mild erythematous reactions in the neck. The masses appeared to subside to a greater degree and more promptly than one would expect from the radiation therapy alone. The patient's hydroxyurea administration began on June 11, 1968 at a rate of 80 mg./kg. every third day as a single dose and continued until his death on August 12, 1969. The patient's total dose of hydroxyurea was 704 grams.

The patient intermittently had a slight decline in his white blood cell count, the lowest being 2,400. This returned to normal with the omission of I or 2 doses of hydroxyurea.

During the last several months of his life the patient developed ulceration of the treatment areas of the left tonsil and posterior tongue, accompanied by infection and swelling of the cheek. This condition responded to appropriate antibiotics and the ulcer almost completely healed. There was no palpable evidence of residual malignancy in the tongue or pharynx.

Subsequently the patient developed a sinus tract from the ulcer in the tonsil bed through the angle of the mandible into the upper neck. He continued to work every day despite this and had practically no pain. The patient developed a sudden hemorrhage, probably due to erosion from the oral ulcer into the carotid artery and died as a result of exsanguinating hemorrhage on August 12, 1969. Autopsy was performed and showed cirrhosis of the liver, accounting for the scan findings. The cause of death was erosion from an oral ulcer into the carotid artery. There was no residual carcinoma found.

Case II. T.B. A 45 year old white man was seen for the first time on June 20, 1968 with a squamous cell carcinoma of the right side of the base of the tongue, 2.5 cm. in diameter. This lesion had a deep excavating ulceration extending into the substance of the tongue for a distance of 4 cm. originating in the vallecula. He was treated with cobalt 60 radiation therapy from June 20, 1968 to August 2, 1968, delivering a total dose of 6,000 rads employing parallel opposed portals. On September 19, 1968, because of a metastatic lymph node in the right upper neck, the patient had a right neck dissection performed. This specimen showed residual degenerated tumor in one lymph node, which had been included in the treatment field. All of the other lymph nodes were negative.

The patient developed an anterior recurrence of his lesion involving the tongue and the floor of the mouth in November, 1968. Between November 14, 1968 and December 20, 1968 he was again treated with cobalt 60 radiation employing parallel opposed lateral portals. A dose of 6,000 rads was achieved in this area using portals which overlapped the previous portals

approximately 50 per cent.

This course of therapy was combined with hydroxyurea at a rate of 80 mg./kg. and over a period of 48 days, from November 14, 1968 through January 1, 1969, a total of 56 grams of the drug was given. The tumor disappeared completely. A slightly greater than average reaction developed in the soft tissues, probably due to the retreatment of the patient rather than a drug reaction.

A moderately severe neuritis was present prior to therapy in the lingual nerve due to the infiltrating nature of the tumor. It persisted after treatment and required a gasserian ganglion injection on December 11, 1968. Large amounts of narcotics were needed.

The patient was febrile throughout the last period of his life. His hydroxyurea administration was stopped because of his general debilitated condition and a leukopenia of 2,700/mm.<sup>3</sup> Bronchopneumonia, aspiration type, developed. The patient expired suddenly on February 6, 1969 as a result of a pulmonary embolus.

Autopsy was performed and the tongue examined at the time of autopsy showed no evidence of any residual tumor and no metastatic disease was found.

Case III. J.Mc T. A 51 year old white man was seen for the first time on October 21, 1966 with a mass lesion in the posterior third of the tongue on the left side involving the lateral border and extending submucosally into the base. It measured  $3\times5\times3$  cm. and the center was ulcerated. Biopsy revealed a squamous cell carcinoma. There was also a 3.5 cm. metastatic lymph node in the left upper neck. The patient's teeth were in very poor condition and he had smoked cigars, a pipe, and cigarettes for many years. No leukoplakia was visible.

Following removal of his teeth the patient was started on radiation therapy. Between October 28, 1966 and December 19, 1966 a dose of 7,000 rads was achieved in the tumor bearing area using parallel opposed lateral portals employing cobalt 60 radiation therapy. The local lesion appeared to regress completely and the patient was scheduled to have a left lateral neck dissection performed.

However, he developed a recurrent mass which measured 4 cm. in diameter and involved the entire left side and part of the right side of the base of the tongue. There was a separate continuous lesion 2.5 cm. in diameter in the left tonsil and an 18 × 30 mm. hard lymph node in the left upper neck.

Additional radiation therapy using cobalt 60 was administered between January 12, 1967 and February 20, 1967 to a dose of 5,500 rads. Hydroxyurea, 80 mg./kg. every third day was administered to a total dose of 70 grams between January 12, 1967 and March 14, 1967. The tumor in the base of the tongue and tonsil disappeared during this therapy and was replaced by an ulcer. The lymph nodes in the left neck remained unchanged and a new lymph node involvement immediately below the first lymph node appeared during the time that the patient was receiving hydroxyurea. It was felt that the hydroxyurea had enhanced the effect of radiation therapy but by itself did not prevent the appearance of a new lymph node involvement outside of the radiation therapy portal. The patient had extreme difficulty with swallowing. He developed bronchopneumonia and expired on April 15, 1967.

#### SUMMARY

Twenty-six cases of advanced carcinoma of the head and neck were treated with hydroxyurea. In 21 cases hydroxyurea and radiation therapy were combined. All cases were in Stages III and IV.

While hydroxyurea did enhance the palliative effect of irradiation in recurrent cases, the best results were obtained in 10 previously untreated cases.

In no case was the tumor permanently controlled by the combined course of therapy but the local and regional responses to treatment were greater than anticipated from radiation therapy alone and in most instances the tumor completely disappeared temporarily.

All of the patients, except 2 currently under therapy, unfortunately have expired as a result of their disease.

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The author acknowledges the kindness of Dr. Gerald Beckloff and Dr. Michael Grozier of the Squibb Institute for Medical Research in supplying the hydroxyurea and Miss Angela Giannotti in typing the manuscript.

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# LARYNGOGRAPHY: THE PROCEDURE OF CHOICE FOR BENIGN LARYNGEAL LESIONS\*

By THOMAS H. JOHNSON, Jr., M.D., and JOHN H. FEIST, M.D. PITTSBURGH, PENNSYLVANIA

CONTRAST laryngography has become an important technique in the diagnosis of malignant laryngeal disease. Additional experience with the method has demonstrated its tremendous importance in evaluation of all laryngeal pathology. The technique comparison study of Thornbury and LaTourette<sup>7</sup> established that laryngography is superior to other roentgen methods in the detection and delineation of laryngeal tumors. We feel that this is also true in the study of benign lesions.

Indirect laryngoscopy and endoscopy yield significant information about disease of the larynx; however, laryngography and motion study techniques add photographic documentation of the anatomic changes and demonstrate the functional physiologic abnormalities. Motion study recording by cine techniques or tape techniques is particularly important in evaluating functional physiology.

#### METHOD

Evaluation of benign laryngeal lesions places a great emphasis on phonation movements and physiology. The anatomy of the contrast laryngogram has been well worked out by those interested in evaluation of malignant lesions. <sup>2,3,6</sup> Meticulous evaluation of physiologic function and its changes over follow-up examinations is as important as anatomic evaluation when benign lesions are studied.

We have routinely used atropine and codeine as premedication to dry up secretions and decrease the cough reflex. As we gained experience with the technique, a significant number of patients did not receive the premedication for various reasons. The studies on these patients were as

adequate as on the patients that received premedication; therefore, we wonder if premedication is absolutely necessary.

Using a spray technique, I or 2 per cent Xylocaine was sprayed into the oropharynx and larynx during oral breathing for topical anesthesia. The contrast medium is then introduced to coat the pharynx and larynx. We prefer a micronized barium and methylcellulose contrast agent. Other contrast agents have been widely used; however, we feel that the barium materials allow a greater clarity of visualization and a more uniform coating.

The patient is placed before the fluoroscope in the posteroanterior position to the screen and with the head directly forward and the chin lifted; fluoroscopy of the larynx is performed to assure coating. If the contrast medium coating diminishes for any reason, it is a simple matter to repeat a spray coat of contrast material. Roentgenograms are obtained in posteroanterior and lateral projections. They can usually be made on a single spot film in the horizontal position using one-half of the film for each view. Concurrent cine strips are also obtained in these positions. One must remember to start and stop the phonation 2 or 3 times while the cine strip is photographing to obtain the greatest quantity of physiologic movement information.

Roentgenograms are made in quiet respiration (QR), phonation of "AH," phonation "EEE," modified Valsalva maneuver (MV), and the "EEE" aspirate maneuver (Fig. 1 through 5). Appropriate lead letters are used to identify maneuvers on the roentgenograms. The modified Valsalva maneuver is performed by requesting the

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<sup>\*</sup> Presented at the Seventieth Annual Meeting of the American Roentgen Ray Society, Washington, D. C., September 30-October 3, 1969.

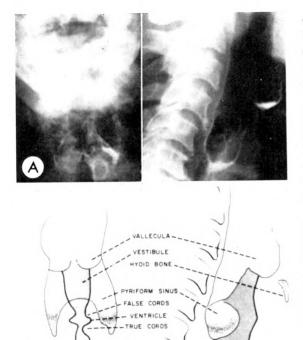


Fig. 1. "EEE" aspirate maneuver. (A) The "EEE" aspirate maneuver is performed during inspiratory phonation of the vowel "E." The vocal cords are stressed downward in the reverse direction, thus yielding information of subglottic lesions. (B) Diagram of A.

TRACHEA

patient to hold his nose and blow out slowly and steadily through pursed lips (as if whistling). The "EEE" aspirate maneuver is performed during the sucking in of air with phonation of the vowel "E." In explanation of this maneuver, it is often easier to communicate with the patient if you explain that the maneuver is performed as if you were "surprised from behind."

A careful evaluation of this routine series of roentgenograms and cine has given us the greatest amount of information with the least difficulty in performance. The patient tolerates the procedure quite well and at times seems to enjoy the mild humor of the solo performance or sing-along situation.

Following completion of study, the patient is instructed to refrain from eating

or drinking for 2 hours until the anesthetic feeling wears off. Postural drainage and other maneuvers are helpful but not often necessary for removal of the contrast medium.

Laryngography in infants and children requires a modification of the adult technique. The pediatric age group is either unable to cooperate or usually unwilling to cooperate during the performance of topical anesthesia for a laryngogram and sometimes the laryngogram study itself.

A small infant feeding tube can be positioned through the nose into the oropharynx or laryngopharynx. The anesthetic agent can be injected through the tube and will spray into the pharynx and larynx without the necessity of instrumentation. One or 2 cc. of anesthetic agent can be introduced by this method for each application. Approximately 3 applications or less

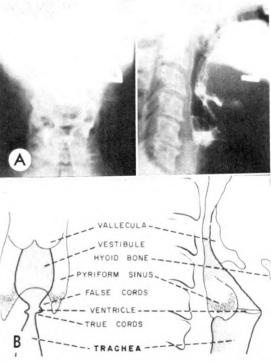


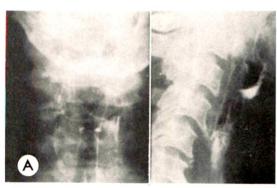
Fig. 2. Phonation of "AH." (A) Phonation of "AH" places partial stress on the vocal cords bringing them toward the midline of the air column. The hypopharynx and tongue are relaxed in this position. (B) Diagram of A.

will be needed for anesthesia in most infants. The contrast material can be introduced through the same tube and will spray adequately to outline the pharynx and larynx.

The random vocalization of infants can be recorded by roentgenography and motion study. This is usually adequate to answer a specific question. Older children are usually cooperative during the phonation movement phase of the examination. Once the anesthetic is introduced and the cough reflex is abolished, the older child is usually cooperative during the performance of the examination.

#### DISCUSSION

Soft tissue roentgenograms of the neck and laminagrams of the larynx have been the traditional roentgenologic investigations of laryngo-pharyngeal problems.



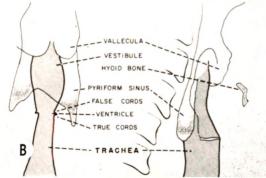


Fig. 3. Quiet respiration. (A) The relaxed view of the larynx is the base-line film for evaluation of anatomy and physiology. The pyriform sinuses are collapsed and the vocal cords are relaxed against the laryngeal wall. (B) Diagram of A.

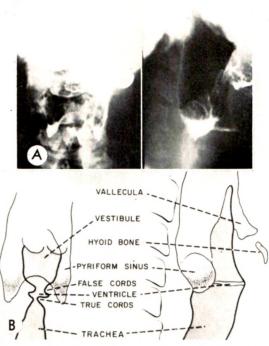


Fig. 4. Phonation of "EEE." (A) Phonation of the vowel "E" places full stress on the vocal cords with hypopharynx and tongue tensed to form the vowel. The pyriform sinuses fill out identifying both inner and outer laryngeal walls. (B) Diagram of A.

Laryngoscopic evaluations yield significant information but are inadequate to evaluate certain areas of the larynx and pharynx. These specific areas are: (1) the larvngeal ventricles; (2) the subglottic space; (3) the thyroid cartilage; (4) the pre-epiglottic space; and (5) the base of the epiglottis.2 Endoscopic evaluation yields no permanent photographic record of the appearance and size of lesions except as described by the examiner or drawn into the record. Endoscopy also yields scanty and sometimes artificial physiologic information. Motion study fluoroscopy or cine fluoroscopy has proven invaluable in physiologic evaluation of the pharynx and larynx.

The technical performance of contrast laryngography has improved markedly in recent years. A spray apparatus for topical anesthesia and contrast medium coating

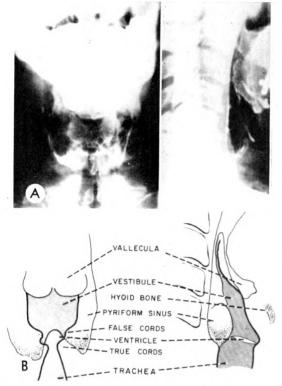


Fig. 5. Modified Valsalva maneuver. (A) This maneuver is performed by holding the nose and blowing out slowly through pursed lips as if whistling. All structures of the larynx and pharynx are ballooned out due to air pressure, demonstrating pharyngeal and laryngeal anatomy. (B) Diagram of A

of the larynx has placed contrast laryngography well within the tolerance range of the average patient. Several patients have commented that a contrast laryngography is a great deal more comfortable than a barium enema examination.

Benign congenital and acquired lesions of the larynx represent an area of medical confusion that is being resolved in our time. Contrast laryngography with cine has proved a useful procedure in evaluation of infant swallowing abnormalities and vocalization difficulties. Laryngomalacia and laryngostenosis are two specific areas where contrast medium studies have documented the lesions and yielded photographic outlines of the lesions for treatment planning (Fig. 6, A and B). Many

rarer benign lesions in infants and children would probably profit by this type of investigation.

Laryngography in the adult has proven extremely useful in the investigation of "hoarseness." Cancerophobia in the hoarse individual is a very real and pertinent finding. Contrast laryngography with cine evaluation is an ultimate step in reassurance of this individual, just as mammography is an ultimate step in reassurance of the female. Hypertrophic laryngitis with its enlargement of the vocal cords and edematous laryngeal changes can be confusing at endoscopic evaluation. The laryngogram is quite characteristic (Fig. 7, A and B).

Paralysis of vocal cord movement can often be documented by cine laryngography without contrast medium, although contrast laryngography will give a better delineation of the abnormality.

Evaluation of benign lesions should include several specific points. The presence or absence of calcifications is important.

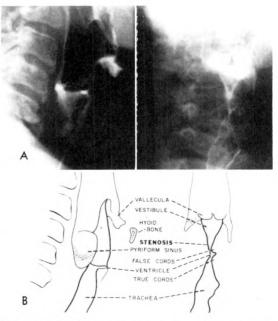
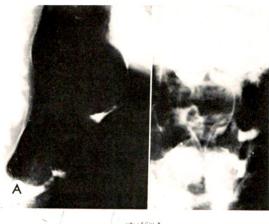


Fig. 6. (A) Post-traumatic laryngeal stenosis is well evaluated by the contrast medium. This patient was in a car wreck and the neck hit the dash board. (B) Diagram of A.



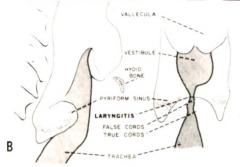


Fig. 7. (A) Hypertrophic laryngitis reveals edematous changes of the cords with swelling of the true and false cords and obliteration of the laryngeal ventricles. (B) Diagram of A.

The gas density, fat density, or water density of the lesions is significant. Compressibility of the structure during phonation is more characteristic of cystic lesions. The regularity or irregularity of the surfaces and borders may be an important point in differential diagnosis between benign and malignant lesions. The presence or absence of infiltration about the lesion may also be an important point in differentiating benign from malignant lesions.

Inflammatory lesions usually produce hypersecretion on the laryngeal surfaces; therefore, mucus material or purulent material may be identified in the contrast outline. The pliability and motion of the cord structures and surface mucosa may be an important point in differentiating noninfected from infected structures; however, both infection and malignancy may cause a loss of pliability and a rigidity of the contrast material coated surfaces.

A final consideration in benign lesions is the exact localization of the abnormality. Localization of the position of lesions is quite easy by contrast laryngography. Localization to intralaryngeal or extralaryngeal areas is of primary importance. Further considerations would be a localization of the lesion to the glottis, supraglottic or subglottic position or a transglottic position involving a combination of these areas.

#### SUMMARY

- 1. Contrast laryngography and cine motion study recording have a definite place in evaluation of benign laryngeal lesions.
- 2. The spray technique of anesthesia and contrast medium application is well suited to this type of study and is quite well tolerated by the patient.
- 3. The series of recorded maneuvers during contrast laryngography of benign lesions should include quiet respiration, phonation of "AH," phonation of "EEE," modified Valsalva, and the "EEE" aspirate maneuver.
- 4. Points in differential diagnosis are discussed.

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# CONTROL BY IRRADIATION OF PERIPHERAL LYMPHATIC DISEASE IN BREAST CANCER\*

By GILBERT H. FLETCHER, M.D. HOUSTON, TEXAS

ACCORDING to the large series of the Christie Hospital of Manchester and the Memorial Hospital of New York City, 4.5 the incidence of disease appearing in the supraclavicular area within the life span of the patients with positive axillary lymph nodes in the surgical specimen is 20 to 25 per cent. Concerning the axillary lymph nodes, the incidence of false negative, i.e., nonpalpable lymph nodes actually infested, is known to be 20 to 30 per cent; conversely, the same percentage of palpable lymph nodes is not found to be positive in the surgical specimen.

At the M. D. Anderson Hospital, patients presenting with breast cancer without evidence of distant metastases (supraclavicular disease not being counted as distant metastasis) fall into the categories of treatment shown in Table 1.

### NONPALPABLE LYMPH NODES

SUPRACLAVICULAR AREA

Table II shows the incidence of supraclavicular disease appearing in the M. D. Anderson Hospital patients with positive lymph nodes in the axillary specimens of radical mastectomy in comparison to 2 large series of patients with positive lymph nodes in the axilla having had no postoperative irradiation.<sup>4,5</sup>

Until about 1958, postoperative irradiation at the M. D. Anderson Hospital consisted of a skin dose of 4,000 rads given in 3 weeks with 250 kv. The tumor dose was at most 3,500 rads, probably less than 3,000 rads at the periphery of the portals

or in the area shadowed by the clavicle. Since 1958 a cesium 137 unit, and since 1963 electron beam or cobalt 60 units have been used for postoperative irradiation. Tumor doses varied from 4,500 rads in 4 weeks to 5,000 rads in 5 weeks. In the patients receiving preoperative irradiation with cobalt 60, the given dose to the supraclavicular area was 4,000 rads and, therefore, the lymph node dose under the skin was approximately also 4,000 rads.

Table II shows a marked decrease in the incidence of supraclavicular disease: 7 per cent with 3,000 to 3,500 rads in 3 weeks and 2 per cent with 4,000 rads or more in 4 weeks.

The incidence of supraclavicular disease appearing later is 3.5 per cent in 491 patients without initial clinical evidence of supraclavicular disease, treated by irradiation for locally advanced disease considered unsuitable for radical mastectomy (Categories III and IV). In these patients, the skin dose to the supraclavicular area was 5,000 rads in 12 weeks with 250 kv. or 5,000 rads given dose in 5 weeks with cobalt

#### AXILLA

Since January 1959, cobalt 60 has been increasingly used in the management of patients with breast cancer. From 1959 through December 1964, there were 52 patients in Category III with no palpable axillary lymph nodes treated with an axillary dose of 5,000 rads in 5 weeks with cobalt 60. Of the 46 patients without recurrence on the chest wall, none had disease in

<sup>\*</sup> Presented at the Fifty-second Annual Meeting of the American Radium Society, Coronado Island, San Diego, California, March

Part of Symposium: The Problems of the Treatment of Lymph Node Metastases from Cancer of the Breast. Moderator, Gilbert H. Fletcher, M.D.

From the Department of Radiotherapy, the University of Texas, M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Taxas

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TABLE I CATEGORIES\* OF TREATMENT FOR BREAST CANCER

	Radical mastectomy, outer quadrant and axilla (-): No postoperative irradiation. Others: Peripheral lymphatics irradiation	II Preoperative irradiation +radical mastectomy†	III Clinically unsuitable for radical mastectomy; radical irradiation or simple mastectomy +radical irradiation	IV Technically unsuitable for radical mastectomy; occasionally radical irradiation, usually rapid palli- ative irradiation
Primary Size	<5 cm.	>5 cm.	<whole breast<="" td=""><td>Whole breast</td></whole>	Whole breast
Skin		Edema or fixation over tumor only	Edema, ulceration, skin fixation < \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	Edema Ulceration Skin fixation Peripheral satellite nodule Massive inllammatory
Pectoral Fascia +Chest Wall			Pectoral fascia fixation	Chest wall fixation
Axillary Lymph Nodes Size	<2 cm.	>2 cm.	Large, with or without limited fixation or multiple	Massive, fixed
Number	Single		or apical	
Location	Not apical	Not apical		Fixed
Supraclavicular Lymph Nodes	ASSESSED TO SERVICE ASSESS		Moveable	TINCA
Staging UICC	$ \begin{array}{c} T_1(N_0,\ N_1) \\ T_2(N_0,\ N_1) \end{array} $	$ \begin{array}{c c} T_1, N_1(+) \\ T_2(+)(N_0, N_1) \end{array} $	$ \left  \begin{array}{c} T_3(N_0,N_1) \\ (T_1,T_2)N_2 \\ (T_1,T_2)N_3 \\ \text{vicular)} \end{array} \right. $	$ \begin{pmatrix} (T_1, T_2, T_3)N_3 \\ T_4(N_6, N_1, N_2, N_8) \end{pmatrix} $
American Joint Committee	$(T_1, T_2)(N_0, N_1)$	$T_2(+)(N_0, N_1(+))$	$\begin{array}{c} T_{\delta}(N_0,N_1) \\ (T_1,T_2)N_2 \\ M \ (Supra clavicular) \end{array}$	$ \begin{array}{c c} T_{3}(+)(N_{0},N_{1},N_{2}) \\ (T_{1},T_{2})(N_{2}(+)) \\ M \ (Supraclavicular) \end{array} $

 $T_{\mathbf{x}}(+)$ , or  $N_{\mathbf{x}}(+)$ : late  $\mathbf{x}$ .  $T_{\mathbf{x}}(N_y, N_z)$ :  $T_{\mathbf{x}}N_y$  and  $T_{\mathbf{x}}N_z$ .

\* The worst feature places the patient in the appropriate category. Multiple features in one category do not change the category. \* Also patients with a disturbed wound from an open biopsy. From: Fletcher et al.: In: Progress in Clinical Cancer. Grune & Stratton, Inc., New York, 1969, pp. 242-256.

the axilla (Table 11). It is a conservative estimate that at least one-third of these 46 patients with advanced local disease had actual involvement of the axillary lymph nodes. Two patients with recurrence on the chest wall developed axillary disease also.

### PALPABLE LYMPH NODES SUPRACLAVICULAR AREA

From 1948 through December 1964, there were 67 patients who had palpable supraclavicular lymph node(s) on admission. Only about half of these lymph nodes were biopsied, since there was no indication to biopsy palpable supraclavicular lymph node(s) to determine the treatment of choice in patients unsuitable for radical mastectomy because of advanced local and/or axillary disease. With 250 kv., 5,000 rads skin dose was given in 10 to 12 weeks followed by 1,000 to 1,500 rads in 1 to 2 weeks through a reduced field over the lymph node(s). With cobalt 60, 5,000 rads given dose was delivered in 5 weeks with 1,000 to 1,500 rads added in 1 week over the lymph node(s) through a reduced portal. Table III shows that a 90 per cent control of the palpable supraclavicular lymph nodes was obtained.

#### AXILLA

From 1959 through December 1964, there were 106 patients in Category III with palpable axillary lymph nodes treated with cobalt 60. The treatment consisted of 5,000 rads in 5 weeks and then, as a rule, 1,000 to 2,000 rads given dose delivered through an appositional portal over the lymph nodes.

Of the 90 patients with no recurrent disease on the chest wall, only I had an axillary failure (Table III). It is a very high control rate, even if 30 per cent of the palpable lymph nodes were not actually involved. Nine of 16 patients with recurrent disease on the chest wall experienced an axillary failure.

TABLE II

CONTROL RATES OF NONPALPABLE AXILLARY AND SUPRACLAVICULAR DISEASE

			Incidence of Appearance	ce After Initial Treatment	And de date of the control of the co		
Axilla (Jan. 1959–Dec. 1964)			Supraclavicular Area (Jan. 1948–Dec. 1964)				
Category III patients 52 5,000 rads tumor dose in 5 wk. with cobalt 60			Axilla+in specimen of radical mastectomy. No postoperative irradiation. Manches-	mastectomy and pre or post- operative irradiation. MDAH	Category III and IV patients 491 without palpable supracla- vicular lymph node(s) on ad-		
	NED C.W.*	Disease on C.W.		699 patients	mission. 5,000 rads skin dose, 12 wk. (250 kv.). 5,000 rad: given dose/5 wk. (cobalt 60)		
No. of patients Failure in axilla		6 2	20-25%	<pre>&lt;3,500 rads/3-4 wk.   (250 kv.)</pre>	3 · 5%		

\* No residual or recurrence in breast or on chest wall.

† JACKSON, S. M. Carcinoma of the breast—the significance of supraclavicular lymph node metastases. Clin. Radiol., 1966, 17, 107-114.

‡ Robbins, G. F., Lucas, J. C., Fracchia, A. A., Farrow, J. H., and Chu, F. G. H. An evaluation of postoperative prophylactic radiation therapy in breast cancer. Surg., Gynec. & Obst., 1966, 122, 979-982.

From: Fletcher, Montague and White: Preoperative radiation therapy in the management of breast cancer. In Frontiers of Radiation Therapy and Oncology, Vol. V. Karger-Basel Publishing Co., White Plains, N. Y. (In Press.)

#### DISCUSSION

The data show that a dose of approximately 4,500 rads in 5 weeks with megavoltage irradiation controls 80 to 90 per cent of nonpalpable aggregates of cancer cells from adenocarcinoma of the breast. If there is no recurrent disease on the chest wall, a high percentage of control of palpable lymph nodes is obtained with tumor doses ranging from 5,000 rads in 5 weeks to 7,000 rads in 7 weeks. When there is a recurrent disease on the chest wall, there is a high incidence of axillary disease, probably

due to reseeding of the axillary lymph nodes.

It has been shown in series of patients with dissection of the internal mammary chain lymph nodes that the lymph nodes infested are usually small, of the order of millimeters; if the lymph nodes were larger than 1 cm., no patient has been salvaged.<sup>6</sup> There is no reason why internal mammary chain lymph nodes of the same order of volume as the axillary and supraclavicular lymph nodes would respond differently to irradiation, and one can, therefore, con-

Table III

CONTROL RATES OF PALPABLE LYMPH NODES ON ADMISSION

106* Category III	Axilla 959–Dec. 1964) Patients with Palp eated with Cobalt	(1	oraclavicular A 948–Dec. 1962	<b>1</b> )	
	NED C.W.‡	Disease on C.W.	67 Patients with Palpable Lymph Nodes		
No. of patients Failure in axilla	1 (1%) 90	16 9	Control Failure	61 6	(90%) (10%)

\*5,000 rads in 5 weeks to 7,000 rads in 7 weeks.

† 5,000 rads to 6,000 rads in 8 weeks with 250 ky.; 6,000 rads to 6,500 rads in 6 weeks with cobalt 60.

‡ No residual or recurrent disease in breast or on chest wall.

clude that a high percentage of small infested internal mammary chain lymph nodes are sterilized with the doses given by the preoperative or postoperative irradiation. This is corroborated by the fact that significant survival rates at 5 and 10 years have been obtained by irradiation only in patients with biopsy proven positive peripheral lymphatics.<sup>3</sup>

#### SUMMARY

Tumor doses of 4,500 rads in 5 weeks are adequate for control of subclinical aggregates of cancer cells from adenocarcinoma of the breast. This dose is well tolerated with negligible, if any, sequelae. Disease in moderate-sized axillary or supraclavicular lymph nodes can be permanently controlled, depending upon the size, by 6,000 to 7,000 rads in 6 to 7 weeks.

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### ENLARGED MASTECTOMY FOR BREAST CANCER\*

REVIEW OF 1,213 CASES

By PIETRO BUCALOSSI, UMBERTO VERONESI, LORENZO ZINGO, and CESARE CANTU MILANO, ITALY

consists of 1,213 cases subjected to enlarged mastectomy between 1948 and 1969.

A brief reference to the technique: enlarged mastectomy comprises dissection of the axillary and internal mammary lymph nodes by an operation involving sternocostal thoracotomy; the thoracic defect is repaired by a flap of the pectoralis major muscle.

The distribution by quadrant is nearly equal: about half of the cases belonged to the medial quadrants and a little under half to the lateral quadrants; the remainder belonged to the central quadrant or to the entire breast (Table 1).

The incidence of lymph node invasion was as follows: 560 cases, or 46 per cent, had no metastases; 386, or 32 per cent, had axillary metastases only; and 267, or 22 per cent, had internal mammary involvement, either with (18 per cent) or without (4 per cent) axillary metastases (Table II).

The distribution of the metastases has been calculated according to the site of the primary tumor: in the outer quadrants the incidence of internal mammary metastases

TABLE I DISTRIBUTION OF CASES BY SITE

Site of Primary Tumor	No. of Cases
Outer quadrants Inner quadrants Central quadrant Whole gland	491 570 130 22
Total .	1,213

HE material covered by this report is lower than in the inner quadrants, whereas it is higher for tumors of the central quadrants (Table III). Of the 50 cases

TABLE II REGIONAL METASTASES TO THE LYMPH NODES IN THE ENTIRE SERIES

Lymph Node Involvement	No. of Cases	Per Cent	
No regional metastases	560	46.2	
Axillary only	386	31.8	
Internal mammary only	50	4.1	
Axillary and internal mammary	217	17.9	22.0
Total	1,213	100.0	

TABLE III INCIDENCE OF INTERNAL MAMMARY METASTASES ACCORDING TO THE SITE OF THE PRIMARY TUMOR

Site	No. of Cases	No. with Internal Mammary Metastases	Per Cent
Outer quadrants	491	69	14.1
Inner quadrant	570	142	24.9
Central quadrant	130	44	33.8
Whole gland	22	12	54.5
Total	1,213	267	22.0

<sup>\*</sup> Presented at the Fifty-second Annual Meeting of the American Radium Society, Coronado Island, San Diego, California, March

From the National Cancer Institute, Milano, Italy.

Part of Symposium: The Problems of the Treatment of Lymph Node Metastases from Cancer of the Breast. Moderator, Gilbert H. Fletcher, M.D.

Table IV

DISTRIBUTION OF REGIONAL METASTASES ACCORDING
TO THE EXTENT OF THE PRIMARY TUMOR

Extent of Primary Tumor	Regional Involvement (histology)	No. of Cases	Per Cent
$T_1-T_2$	No metastases Axillary only	516 313	50.2 30.4
(84.7%)	Internal	43	4.2
(04.770)	mammary only Axillary and internal mammary	156	15.2
	Total	1,028	100.0
T <sub>3</sub> -T <sub>4</sub>	No metastases	44	23.8
(15.3%)	Axillary only Internal	73 7	39·4 3.8
	mammary only		
	Axillary and	(-	
	internal mammary	61	33.0
	Total	185	c.∞1

Table V

DISTRIBUTION OF REGIONAL METASTASES ACCORDING
TO CLINICAL EXAMINATION OF THE AXILLA

	<del></del>		
Clinical Examina- tion	Regional Involvement (histology)	No. of Cases	Per Cent
N <sub>0</sub>	No metastases Axillary only Internal	404 147	61.2
(54.4%)	mammary only	40 69	6.1
	Axillary and	69	10.4
	internal mammary		
	Total	660	100.0
	No metastases	156	28.2
	Axillary only	239	43.2
$N_1$	Internal	IO	1.8
(45.6%)	mammary only Axillary and internal mammary	148	26.8
_	Total	553	100.0

withisolated internal mammary metastases, 33 belonged to the medial quadrants, and 17 to the central or lateral quadrants.

Regional invasion according to the extent

of the primary tumor is shown in Table IV.

Of 660 cases with clinically negative axillary lymph nodes only 61 per cent had no regional metastases at histologic examination; the others had axillary or internal mammary spread. This shows how poor the correlation is between clinical assessment and histologic examination of the regional lymph nodes (Table v).

Of the cases with clinically positive lymph nodes, 28 per cent were histologically negative for the various regional lymph node groups.

Table VI 5 year survival according to regional spread

Regional	No. of	5 Year	Per
Involvement	Cases	Survival	Cent
No metastases Axillary only Internal mammary only Axillary and internal mammary	285	233	81.7
	171	95	55.6
	28	22	78.6
	126	35	27.8
Total	610	385	63.1

Table VII
5 YEAR SURVIVAL ACCORDING TO THE EXTENT OF THE PRIMARY TUMOR

Extent	Cases	5 Year Survival	Per Cent	
T <sub>1</sub> -T <sub>2</sub> T <sub>8</sub> -T <sub>4</sub>	507 103	34 <sup>0</sup> 45	67.1 43·7	
Total	610	385	63.1	

Table VIII
5 YEAR SURVIVAL ACCORDING TO CLINICAL EXAMINATION OF THE AXILLA

	No. of	5 Year	Per		
	Cases	Survival	Cent		
N <sub>0</sub>	327	237	72.47		
N <sub>1</sub>	283	148	<b>52.2</b> 9		
Total	610	385	63.1		

Table IX
5 year survival according to clinical and histologic assessment of regional spread

Clinical Diagnosis	Histologic Diagnosis	No. of Cases	5 Year Survival	Per Cent	
	No metastases	207	171	82.6	
	Axillary only	59	37	62.7	
$N_0$	Internal mammary only Internal mammary	24	19	79.2	
	and axillary	37	10	27.0	
	Total	327	237	72.5	
	No metastases	78	62	79.5	
	Axillary only	112	58	51.8	
$N_1$	Internal mammary only Internal mammary	4	3	(75.0)	
	and axillary	89	25	28.1	
	Total	283	148	52.3	

Five year survival was calculated on 610 cases operated on up to 1964. Fifteen patients lost to follow-up were regarded as dead. The total 5 year survival was 385 out of 610 cases, that is 63.1 per cent. What is important and was unexpected by us is that prognosis is excellent in cases with internal mammary metastases only (Table vI).

Assessing the size of only the primary tumor, we have analyzed the material according to the clinical status of the axillary lymph nodes (Table VII).

In N<sub>0</sub> cases survival was 72 per cent and in N<sub>1</sub> cases 52 per cent (Table VIII).

The cases with clinically palpable but histologically negative lymph nodes showed no better long-term results than the others,

Table X
5 year survival according to the site of the primary tumor

Site of Primary Tumor	No. of Cases	5 Year Survival	Per Cent		
Inner half Outer half Central Whole	316 198 79 17	206 124 50 5	65.2 62.6 63.3 29.4		
Total	610	385	63.1		

as other investigators have found (Table IX).

With regard to survival in relation to the site of the primary tumor, no significant differences were observed between tumors of the lateral and those of the medial quadrants (Table x).

The cases were then divided into 3 groups by type of complementary radiotherapy: (1) the first series (1948–1958) of 199 cases was treated by enlarged mastectomy plus postoperative radiotherapy (3,000 r). (2) In the second series (1959–1963) only the

TABLE XI
5 YEAR SURVIVAL ACCORDING TO
POSTOPERATIVE RADIOTHERAPY

	No. of Cases	5 Year Sur- vival	Per Cent
First Series			
Systematic Postoperative			
Radiotherapy	199	112	56.3
Second Series			
Selected Postoperative			i
Radiotherapy	304	200	65.8
(only to cases N+)			_
Third Series			
No Postoperative			
Radiotherapy	107	73	68.2

Table XII
5 YEAR SURVIVAL IN CASES TREATED WITH POSTOPERATIVE RADIOTHERAPY AND IN CASES
TREATED ONLY SURGICALLY ACCORDING TO REGIONAL INVOLVEMENT

	I Series Postoperative Radiotherapy All Cases			II Series Postoperative Radiotherapy to N+		III Series No Postoperative Radiotherapy			
	No. of Cases	5 Year Survival	Per Cent	No. of Cases	5 Year Survival	Per Cent	No. of Cases	5 Year Survival	Per Cent
No metastases Axillary only Internal mam-	81 70	66 33	81.5 47.1	154 64	124 · 38	80.5 59·4	50 37	43 24	86.0 64.9
mary only Axillary and internal	3	3	(100.0)	21	16	76.2	4	3	(75.0)
mammary	45	10	22.2	65	22	33.8	16	3	18.8
Total	199	112	56.3	304	200	65.8	107	73	68.2

N+ cases, that is those with positive regional lymph nodes, received complementary treatment. (3) The cases of the third series were treated surgically only. This series of cases forms part of an international cooperative study which collected from 1964 to 1966 about 2,000 cases, half being treated by radical mastectomy and the other half by enlarged mastectomy, without complementary radiotherapy.

The results of the 3 series are given in Tables XI and XII. Broadly speaking, the cases of the third series, without postoperative radiotherapy, showed better long-term results than the 2 series treated with postoperative radiotherapy. The most surprising datum is that the cases with axillary metastases treated only by surgery showed a higher rate of survival than those receiving postoperative radiotherapy. It should be pointed out, however, that the treatment was not randomized in this

series, and so the results are subject to the usual criticisms about comparing series treated at different periods.

#### SUMMARY

It may be concluded from the whole case material that:

- 1. About 22 per cent of the women with operable breast cancer had internal mammary metastases.
- 2. Even tumors of the lateral quadrants rarely metastasize to the internal mammary lymph nodes.
- 3. Survival among cases with internal mammary metastases only is very high (70-80 per cent at 5 years).
- 4. In our experience postoperative radiotherapy did not improve the 5 year survival.

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# PRESENT STATUS OF THE MANAGEMENT OF REGIONAL LYMPH NODES AND PLANNED CLINICAL TRIALS\*

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THE controversy which exists regarding the primary treatment of breast cancer is, at least in part, the consequence of conceptual changes which have resulted from new information relative to tumor biology. Our knowledge concerning tumor dissemination and metastases formation, while still exceedingly incomplete, is well beyond that of Halsted's time. To continue to look upon the regional lymph node merely as a divine improvisation for the trapping of tumor cells is an anachronism! Accumulating information, both clinical and experimental, suggests that our conventional surgical attitude towards the lymph nodes may need reassessment. The consideration that negative lymph nodes imply that tumor cells have not spread. whereas positive lymph nodes are the hallmark of dissemination, may be an oversimplification. To be certain, it well may be that the negative lymph node indicates that no cells have been dispersed; but, there may be alternative explanations for such a finding. It has been recognized since Paget's time (1870),17 but consistently ignored in surgical thinking, that lymphatic metastases may appear in distant rather than more proximal lymph nodes. This phenomenon of "skip" metastases is related to direct lymphatic communication and the dynamics of the lymph flow in the area involved. Such bypasses can explain the noninvolvement of individual lymph nodes and atypical distribution of lymphogenous metastases. The concept originally expressed by Bartels in 1909 that lymph does not reach the blood without passing through at least one lymph node,1 despite evidence to the contrary, still prevails. It has been established that in addition to being carried to regional lymph nodes, tumor cell emboli may bypass such lymph nodes to directly enter the thoracic duct and be conveyed to veins at the base of the neck from which point they are bloodborne. Controversy has existed concerning the magnitude and significance of other lymphaticovenous pathways throughout the body. This has been particularly so relative to the presence of such connections in lymph nodes and the part which they play in the entry of tumor cells into the blood stream. Recent studies from our laboratory support the existence and possible importance of such communications in tumor cell dissemination. Evidence by others would seem to substantiate such an event.

Recently, we have challenged the concept that lymph nodes act as an effective barrier to tumor cell dissemination. Data obtained by us in this regard support the conclusion that the lymph node is not as effective a barrier to tumor cells as formerly believed. The majority of tumor cells entering the lymph nodes may fail to maintain permanent residence. Moreover, information obtained with erythrocytes or other particulate matter has little relevance to the fate of the tumor cells.6-8

Evidence implicating immunologic mechanisms in the fate of tumors provokes other considerations. Should a human neo-

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plasm contain tumor antigens which evoke a host immune response—a situation no longer considered to be remote—it would seem reasonable to anticipate, that, when cells from a tumor become disseminated via lymphatics, they could possibly be destroyed by the immune lymph node. Experimental evidence obtained both in vivo and in vitro in support of the tumor cell destructive properties of sensitized lymphocytes makes feasible such a possibility. Recent information relative to cell kinetics suggests that it may be possible that a small number of disseminated nonproliferative cells may find their way to a lymph node where they lodge to remain nonproliferative and unobserved for varying periods of time, i.e., the dormant tumor cell. Thus, it may very well be that there are other reasons for the finding of the negative lymph node than that which suggests that no tumor cells have been dispersed.

Similarly, there may be other reasons for the presence of the positive lymph node. Conventionally, the presence of a tumorcontaining lymph node is considered simply to be the result of tumor cells having disseminated via lymphatics, with their subsequent lodgement and growth in lymph nodes. This may represent an oversimplification. Perhaps only when the number of disseminated cells, i.e., the challenge dose, exceeds the capability of the lymph node for cell destruction or, alternatively, there is a reduction of the immune capabilities of the lymph node and/or possibly a change in the biologic nature of the tumor cell, does tumor grow in the lymph node. It has been well demonstrated in animal systems that all tumor immunity can be overcome when the challenge dose is of sufficient size.

Thus, the presence or absence of tumor in lymph nodes may not be of as great significance as was believed in the determination of lymphatic tumor cell dissemination. Since, as it is well known, there is a better prognosis in cancer patients when lymph nodes are not involved, such an hypothesis after cursory consideration may not seem to be reasonable. It may be, how-

ever, that positive lymph nodes merely denote that the disseminated cells which produced such growth as a result of intrinsic cell properties and/or host factors are capable of developing metastases in other parts of the body as well. Negative lymph nodes may merely reflect conditions which, in addition to preventing nodal growth of tumor, also inhibited metastases from occurring in other places. Thus, it may be possible that the patient with negative lymph nodes is the one whose immune competence is entirely adequate to eliminate disseminated tumor cells thereby preventing secondary tumor growth and that this is the reason for the more favorable prognosis in such patients.

There are inklings clinically which suggest that all is not right with our conventional thinking relative to the lymph node. Recent examination of data collected by the National Surgical Adjuvant Breast Project (NSABP) has revealed that the range of the number of lymph nodes examined from radical mastectomy specimens at 45 institutions was remarkably great, the median number varying from a low of 7 at one institution to a high of 28 at another. The range in the number of lymph nodes per specimen is apparently related to a combination of anatomic differences, errors in identification of all lymph nodes by the pathologist, and possible variations in the extent of surgical dissection. Despite these seeming inaccuracies, the results failed to demonstrate that the discovery and examination of a greater number of lymph nodes in a specimen were more meaningful in determining prognosis than if only a few were recovered. Patients with 5 or 10 lymph nodes reported as negative had essentially the same recurrence or survival rate as did those with 25 or 30 lymph nodes free of tumor. Thus, the concept of the latter representing a "purer" negative group was not substantiated. Likewise, when specimens with positive lymph nodes contained I to 5 or more than 30 lymph nodes, recurrence and survival rates were similar. The patient with 2 positive lymph nodes out of 5 examined was not found to be at a greater risk than another having 2 with tumor out of 30 recovered. Such findings, while contrary to current thought, provoke certain considerations relative to the lymph node which cannot be dismissed without further evaluation.

In another analysis of the same data, it was demonstrated that there was no significant increase in recurrence rate in patients treated by conventional radical mastectomy when their lesions were located in the inner half or central portions of the breast, in spite of the acknowledged greater incidence of internal mammary lymph node involvement.10 If patients with positive axillary lymph nodes in the study had an incidence of internal mammary lymph node involvement similar to that noted by Cáceres, Handley, 12 and others, how could the observed similarity of recurrence and survival with the inner and outer quadrant lesions be explained when such lymph nodes were left untouched? It would seem that the presence of positive internal mammary lymph nodes in addition to axillary lymph node involvement may be of no more biologic or prognostic significance than if axillary lymph nodes alone are involved. Only if occult metastases exist elsewhere than in lymph nodes with the same frequency in patients with dual lymph node involvement, i.e., internal mammary and axillary, as in those with axillary lymph node involvement alone, can the findings of similar prognosis regardless of tumor location be explained.

Whether secondary embolization will occur from a lymph node which has acted as a temporary barrier to tumor spread has, in my opinion, not been satisfactorily elucidated. Should it occur, there is reason to suspect that it is of little significance in so far as the fate of the patient is concerned. The demonstration by Paterson and Russell<sup>18</sup> that irradiation was of equal value if given in the immediate postoperative period or when recurrences became apparent is suggestive of this.

Recently, the possibility has been con-

sidered that the regional lymph nodes in a tumor-bearing host possess special immunologic properties and should be preserved rather than removed with the primary tumor. Such studies specifically related to the importance of the regional lymph node in tumor immunity are few in number. Our laboratory is involved in a program aimed at determining the validity of such a concept. Preliminary data would suggest in several model systems that: (1) the regional lymph node facilitates the initiation of tumor immunity; (2) the regional lymph node may contribute to the maintenance of immunity; and (3) surgical trauma may be capable of depressing immunity.

The controversy which exists in this country and throughout the world relative to the proper primary treatment for clinically curable female breast cancer may, in part at least, be related to the accumulating information in both the laboratory and clinic described above. Whereas a decade or two ago treatment by radical mastectomy was virtually unchallenged and accepted as standard therapy, there is at present serious doubt by many concerning the efficacy of such surgery. It is almost tragic that such an important issue has, to the present time, been decided by individual surgeons primarily as a result of emotionalism, information obtained from insufficiently carried out retrospective analyses of case records and by comparisons of data obtained from divergent series of patients. Moreover, as so frequently happens, popularity has borne to many the connotation of excellence. Women with breast cancers may have surgical procedures ranging from extended radical mastectomy with internal mammary dissection to a "lumpectomy" depending on the belief of the surgeon. For the same reason, they may or may not receive one of several ancillary therapeutic modalities.

Recently, I have had the opportunity to review all of the available information which supports or denies the worth of the various alternatives available for the primary treatment of invasive breast cancer. Neither time nor space provides an opportunity to document in detail the findings. The following comments summarize my conclusions relative to the various modalities. After a careful analysis of the works of Halsted, it seems obvious that the surgical principles laid down by him were properly conceived in keeping with his knowledge of tumor biology, and, in particular, tumor spread. If, since his time, as a result of accumulation of new information relative to the phenomena of metastases—and it cannot be denied that this has occurred—new concepts have arisen; then, either the original surgical principles which he formulated have become anachronistic or if they are still valid, they were conceived originally for the wrong reasons.

Dissatisfaction with the results of radical mastectomy—and who can be satisfied—at present can lead only to the employment of a few surgical alternatives.

By continuing to be progressively more precise in defining criteria of operability so that ultimately only the most favorable cases are subjected to radical mastectomy, the results with this procedure will undoubtedly improve. Such restrictions, however, would be self-defeating and are unrealistic for, while the operative results would become more favorable, more and more patients would be denied the opportunity for "proper" treatment. Another alternative is to employ a more radical surgical approach. It would be hoped that superradical surgery utilizing the same criteria of operability employed for radical mastectomy would result in a greater disease free survival rate and/or would permit the extension of criteria of operability so that patients presently considered unsuitable for conventional radical mastectomy would become candidates for cure by extended surgery. As an alternative to conventional radical mastectomy, the use of a less extensive surgical procedure could be considered. It could be argued that the results achieved by radical mastectomy are not entirely the

consequence of the surgery per se, but are more related to host tumor factors and that a lesser operation will make the same contribution to the equation which determines results, as does more extensive surgery. Such surgery alone cannot extend the criteria of operability, it may only equal or possibly improve upon results obtained utilizing the same criteria. It must be emphasized that, whereas a lesser surgical procedure may not produce results as good as radical mastectomy when utilized on patients having tumors which fit one set of operative criteria, it may be equal or better if the criteria are different. Lastly, the results of radical mastectomy utilizing the same operative criteria may be improved and/or the criteria for surgery may be broadened by employment of surgical adjuvant therapy such as irradiation. oophorectomy, chemotherapy, and other systemic therapy.

Radical Mastectomy. In my opinion, the results of radical mastectomy, like the results of all experiments, are inherently provisional in nature. Since it has not been demonstrated that radical mastectomy has cured all patients with breast cancer, no matter what the stage of the disease, such a procedure can serve its purpose only as a temporary "control" against which another promising therapeutic modality may be compared. When another therapy has been found to excel over radical mastectomy, then it should serve as the "baseline" for comparison. Only by such an orderly sequence of trials will progress be made in a reasonable period of time. Let us briefly consider some of the alternatives to radical mastectomy.

Extended Radical Mastectomy. Conceptually, the extended radical mastectomy is in keeping with present day thinking concerning cancer surgery; and, if these thoughts are valid, then such surgery should be rewarding. From a thoroughly objective and unbiased analysis of all the reports which deal with this subject, it is this reviewer's opinion that there is no definite evidence to substantiate the worth of such surgery

despite its protracted employment. The extremely low mortality and morbidity reported in most of the series attest to the magnificent gains which have been achieved both in the technical and supportive aspects of surgery in general. If there are those who still believe that extended radical surgery should be carried out in the treatment of breast cancer, and I do not, then the burden of proof of the value of the procedure falls upon them. Only can they prove its worth with a properly controlled prospectively randomized study evaluating this procedure with more conventional surgery in similar patients. Only in such a setting with such objectives will further employment of super-radical surgery appear justified. To continue to subject patients to such operative procedures for another decade or two and still not have any more exact information than exists today, in my opinion, would be meaningless and ill-advised.

Modified Radical Mastectomy. Evaluated objectively, it certainly seems that there is no adequate evidence to justify the "popularity" which this procedure is gaining. Once again, it would seem that a therapeutic modality is gaining prominence for reasons other than its proven worth. For the surgeon who treats the occasional patient with breast cancer to begin to use this procedure because it seems "reasonable," is completely unjustified. Until evidence is secure that the procedure is worthy of general use, its employment for less sound reasons will only prolong and accentuate the present era of therapeutic uncertainty. This reviewer personally believes that the results with modified radical mastectomy will, in all probability, be equivalent to those with radical mastectomy when employed in equivalent patients and I would look in favor upon the procedure. Conceptually, I am in agreement with Handley and others who support such surgery. 18,19,20 Consequently, the sooner a properly conducted prospective randomized trial is carried out to evaluate the worth of this procedure, the sooner its use can be absolutely justified. Those who are advocates of this operation can prove that they are or are not correct by participating in such a study which will result in conclusive evidence. There can be no other way.

Simple Mastectomy. In my opinion, no one has unequivocally demonstrated clinically that simple mastectomy is a procedure which should or should not supplant radical mastectomy. The findings of Mc-Whirter<sup>14–16</sup> and Crile<sup>3–5</sup> are of great historic interest in that they have provided suggestive evidence which makes further evaluation desirable. There is no more justification to condemn simple mastectomy than there is to recommend its use to the exclusion of other procedures. So far as I am concerned, biologic considerations are even more compelling than clinical ones to suggest that simple mastectomy should be an equivalent procedure to radical mastectomy and that immediate prospective trials to affirm or deny this thesis must be carried out without delay.

Local Excision. From a complete review of all information available in regard to local excision of breast cancer, it would be my feeling that, at this point in time, more than speculation with this type of therapy is not warranted unless it involves a rigidly controlled clinical trial. In my opinion, it is justified only as part of a cooperative study.

Radiation Therapy. Just as after almost three-quarters of a century there is indecision concerning the type of surgery which is best for the treatment of breast cancer, so is there uncertainty concerning the merits of radiotherapy as an adjunct to surgery. Because of this uncertainty, the NSABP began a randomized prospective trial with a specific protocol to determine the worth of postoperative radiotherapy in 1961. Just at the present time have the results of this study become known.11 Patients received radiotherapy to their parasternal, axillary, and supraclavicular regions immediately following radical mastectomy. In brief, it was observed that there was no significant difference in treatment failure or survival

rates between all patients receiving radiotherapy and those serving as controls at 3, 4, or 5 years following surgery.

#### COMMENTS

Just as the prime purpose of laboratory investigations is to provide suggestions as to what might be expected to occur when such studies are applied to the human, so may the results of retrospective analyses supply hints for future definitive evaluation. Consequently, the findings of Crile, McWhirter, Patey and others are of such a nature. They have provided "suggestive" evidence which should be accepted as such. The next step, as a result of these intimations, is the carrying out of properly conceived prospective clinical trials with randomization of similar patients so that one group receives the therapy to be evaluated and the other, which serves as a control group, is the recipient of the present "standard" therapy. Utilizing such a procedure, the worth of a therapy can be known with a high degree of certainty in the shortest possible time prior to its being carried out on the population as a whole. Since my comments would suggest that the validity of almost all therapeutic modalities relative to the treatment of breast cancer remain tenuous, the surgeon may legitimately ask what he is to do when he encounters a patient needing treatment. Indeed, he is faced with a dilemma.

#### CONCLUSION

Obviously, until breast cancer can be prevented or a systemic therapy becomes available which can totally eradicate the primary tumor and its metastases, surgical removal of the tumor will remain the fundamental basis of therapy. How extensive the surgery should be, however, remains uncertain. Since it is unlikely that further gains will be accomplished by surgery alone but will be the result of adjuvant therapy, he may ask, what adjuvant therapy? Again the answers are uncertain.

It is my belief and I cannot emphasize this too strongly, that at the present time it is the obligation of any surgeon who is performing breast cancer surgery in an institution capable of carrying out clinical trials as part of a cooperative group to participate in such a program. Teaching hospitals, clinics, and cancer institutes, are all particularly suited for such an undertaking. The NSABP has been established for such a purpose. It provides the opportunity for such cooperative endeavors having as their objective the clinical evaluation of the worth of certain modalities already employed and those which may in conjunction with surgery improve results. Those institutions whose members recognize the urgency of such an effort are invited to participate.

Those, who for one reason or another are unable to participate in such trials—aside from doing everything in their power to encourage them—should continue to treat patients in their conventional fashion until the results of these trials are made known.

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## SIGNIFICANCE OF INTERNAL MAMMARY LYMPH NODE METASTASES IN BREAST CANCER\*

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THE lymphatic drainage of the breast extends into 2 primary depots: the axilla and the internal mammary lymph node chain. Although anatomic studies8 demonstrate that \ of the lymphatic drainage of the breast extends into the axilla and ½ into the ipsilateral internal mammary chain regardless of the site of dye injection into the breast, several clinicians<sup>1,6</sup> have shown that primary breast cancer arising in the central and inner portions of the breast spreads more frequently and at an earlier stage to the internal mammary lymph nodes than do similar lesions arising in the outer portion of the breast. Others<sup>2,7</sup> have demonstrated a higher local recurrence rate and a lower salvage rate with medial lesions when compared with breast cancers of similar size, grade and clinical stage arising in the lateral portion of the breast, following radical mastectomy11 (Tables I and II). It has also been shown that parasternal chest wall recurrences arising from internal mammary lymph node metastases and presenting as the first sign of recurrent cancer, not infrequently can be treated successfully by radical surgical excision or by aggressive supervoltage radiation therapy—with resultant longterm salvage free of disease.9

#### MATERIAL AND RESULTS

During the last 20 years<sup>10</sup> we have resected the internal mammary lymph nodes routinely by monobloc excision in patients with a high risk of internal mammary disease—primarily those with lesions presenting in the medial and central portions of the breast. Careful follow-up of these patients has given us a unique opportunity to evaluate the incidence of internal mammary metastases for the various sectors of the breast (Fig. 1) and to correlate these data with the subsequent clinical course of the disease.

We have now performed 725 extended radical mastectomies at the Memorial Center (Table III). Selection of patients with medial and central lesions has resulted in a relatively high take of internal mammary lymph node disease; although only 47 per cent of the group shows axillary involvement, 33 per cent shows internal mammary involvement. Only the internal mammary lymph nodes were positive in 8 per cent of these patients. In the over-all group more than 55 per cent showed metastatic lymph nodes, either in the axilla or the internal mammary chain or both. Review of these data demonstrates that primary lesions arising in the parasternal sector of the breast spread to either the internal mammary lymph nodes or the axillary lymph nodes with equal facility. As the location of the primary tumor moves lateralward in the breast, the relative involvement of internal mammary versus axillary lymph nodes diminishes, so that almost no lesions presenting in the

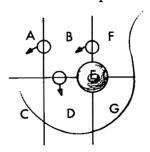


Fig. 1. Diagram of the sectors into which the breast is divided.

<sup>\*</sup> Presented at the Fifty-second Annual Meeting of the American Radium Society, Coronado Island, San Diego, California, March

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Table I incidence of parasternal chest wall recurrence as the first sign of recurrent cancer in 1,000 patients treated by radical mastectomy between 1940 and 1945

Sector	No. of Cases	Parasternal Chest Wall Recurrences
A Axillary Lymph Nodes— Axillary Lymph Nodes+	65 35 30	5 14% 6 20%}11 17%
B Axillary Lymph Nodes— Axillary Lymph Nodes+	251 118 133	10 8% 8 6%}18 7%
C Axillary Lymph Nodes— Axillary Lymph Nodes+	29 14 15	1 7% 6 20%
D Axillary Lymph Nodes— Axillary Lymph Nodes+	69 22 47	1 5% 4 8%} 5 7%
E Axillary Lymph Nodes— Axillary Lymph Nodes+	84 25 59	° °% 2 3%} 2 2%
F Axillary Lymph Nodes— Axillary Lymph Nodes+	416 135 281	2 2% 6 2%} 8 2%
G Axillary Lymph Nodes— Axillary Lymph Nodes+	86 25 61	I 4% 2 2%

Total—5% Parasternal Chest Wall Recurrences. 1,000 Determinate Cases.

outer quadrant with negative axillary lymph nodes show internal mammary lymph node involvement.

This incidence of internal mammary lymph node disease for each of the various sectors of the breast corresponds closely to the incidence of parasternal recurrence as the first sign of recurrent cancer following radical mastectomy, as demonstrated in a series of 1,000 cases treated between 1940 and 1945. In this group, a parasternal recurrence appeared as the first sign of recurrent cancer in 5 per cent of the over-all group. Parasternal recurrence was noted as the first sign of recurrent cancer in 18 per cent of the primary lesions presenting in the parasternal sectors, in 7 per cent of lesions presenting in the sectors between the mid-

line of the breast and the parasternal sector and fell to only 2 per cent for the outer half lesions (Table 1). The closer the primary breast cancer arises to the sternal margin of the breast, the greater the risk of internal mammary lymph node metastases—all other factors being equal.

Internal mammary lymph nodes are found with decreasing frequency as one goes from the first to the fifth interspace: 88 per cent in the first interspace; 84 per cent in the second; 73 per cent in the third; 46 per cent in the fourth; and only 12 per cent in the fifth (Table IV). These lymph nodes are found with equal frequency medially or laterally to the internal mammary blood vessels. The distribution of the internal mammary lymph nodes contain-

 $Table\ II$  5 year survival rate free of disease for 1,000 patients with primary operable breast cancer treated by radical mastectomy at memorial center for cancer and allied diseases from 1940 to 1945

Sector	No. of Cases	5 Year Survival
A	65	
Axillary Lymph Nodes-	35	19 54% 6 2c% 25 38%
Axillary Lymph Nodes+	30	6 20% 35 38%
В	251	_
Axillary Lymph Nodes—	118	84 71% 55 41%
Axillary Lymph Nodes+	133	55 41% \\ 139 30 \\
С	29	
Axillary Lymph Nodes-	14	11 78% 4 26%
Axillary Lymph Nodes+	15	4 26% } 13 32/6
D	69	
Axillary Lymph Nodes-	22	$\begin{bmatrix} 17 & 77\% \\ 18 & 38\% \end{bmatrix}$ 35 51%
Axillary Lymph Nodes+	47	18 38% 35 5176
E	84	
Axillary Lymph Nodes-	25	21 84% 32 38%
Axillary Lymph Nodes+	59	11 19% 32 30%
F	416	
Axillary Lymph Nodes-	135	110 81%) 89 32%} 199 48%
Axillary Lymph Nodes+	281	89 32% (199 40%)
G	86	
Axillary Lymph Nodes-	25	21 84% 19 31%} 40 47%
Axillary Lymph Nodes+	61	19 31% (40 4)%
Over-all 5 Year	Survival Rate (including Pag 1,000 Determinate Cases	et's disease)
Axillary Lymph Nodes-	374	283 76%)
Axillary Lymph Nodes+	626	28376% $48.5%$

Table III

LYMPH NODE METASTASES IN PATIENTS TREATED BY EXTENDED OPERATION

Location	A	В	l c	D	E	172	G	T	otal
Location	Α.	D		ט	E	F	G	No.	Per Cent
Total No. of Cases	200	285	67	73	66	26	8	725	100
All Lymph Nodes Clear	115	137	23	31	11	5	2	324	45
Interal Mammary Only Involved	24	17	11	6	1	I	0	60	8
Axillary Only Involved	2.3	71	10	14	31	11	4	164	23
Both Axillary and Internal Mam- mary Involved	38	60	- 23	. 22	23	9	2	177	25
Over-all Group Lymph Nodes Positive 55.4%			32.7 47 8.3	% all ly % +in % +ax % only % with	ternal r tillary interna	namma ıl mamı	mary	-	
· .								ph node	:3

ing metastatic breast cancer is quite different. The highest incidence appears in the second interspace (19 per cent); then the third (17 per cent); the first (16 per cent); the fourth (6 per cent), and finally only 2 per cent in the fifth interspace. Lymph nodes lying medial to the internal mammary vessels are involved just as often as are those lying lateral to the internal mammary vessels.

Patients with metastases in the internal mammary lymph nodes can be salvaged by radical surgical excision of the lymph node complex just as those with axillary metastases are salvaged by adequate axillary dissection. Five hundred consecutive patients with primary operable breast cancer were operated upon more than 5 years ago (Table v): 47 per cent had axillary lymph node involvement and 30 per cent had internal mammary lymph node involvement. A 5 year salvage rate of 73.4 per cent was attained in this group, with more than 65 per cent clinically free of disease at 5 years. Patients with only internal mammary lymph node involvement did almost as well as those with only axillary

Table IV

FREQUENCY OF INTERNAL MAMMARY LYMPH

NODES IN INTERSPACES

(500 Patients)

T	% Lymph Nodes Found				Positi	
Inter- space	Total			Total		
	Med		Lat	Med		Lat
I	69	88	72	10	16	10
2	61	84	60	12	19	11
3	52	73	49	12	17	12
4	28	46	33	3	6	5
5	5	12	9	0.8	1.6	0.8

#### TABLE V

# EXTENDED RADICAL MASTECTOMY 5 Year Survival Rates 500 Patients (1051-1064)

30% internal ) (65.4% NED	500 Landin	3 (1951 1904)
	30% internal	(65.4% NED
mammary+ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	mammary+(	73.4% survival
47% axilla+ 7.0% local		7.0% local
54% lymph nodes+) recurrence	54% lymph nodes+	recurrence

Lymph Nodes	No. of Patients	NED	Survival
All clear Only axilla+ Only internal mammary+ Both axilla and internal mam- mary+	228 124 36 112	80 % 62 % 53 % 43 %	87 % 68 % 64 % 54 %
Total*	5∞	65.4%	73.4%

NED-no evidence of disease.

involvement—more than 60 per cent alive in both groups at 5 years. When the disease was more extensive and had spread into both the axillary and internal mammary lymph nodes, 43 per cent of patients were clinically free of disease 5 years following surgery. At 10 years following the extended radical mastectomy, 54 per cent of 315 patients with approximately the same lymph node involvement were clinically free of disease (Table VI). When either only internal mammary lymph nodes or only axillary lymph nodes were involved, 52 per cent of patients were free of disease 10 years following the extended operation. This salvage rate drops to 20 per cent when both lymph node areas contain metastases. These data are not corrected for age or intercurrent disease.

Of the original group undergoing the extended radical mastectomy, 8 per cent developed a new primary cancer in the opposite breast and 7 per cent died of intercurrent disease, clinically free of breast cancer (all are included in the Tables). Although patients with internal mammary lymph node metastases are salvaged long-term wise by aggressive surgical excision and/or supervoltage radiation therapy, there is no doubt that the presence of metastases

<sup>\*</sup> Includes 14 patients dead with no clinical evidence of breast cancer.

Table VI

EXTENDED RADICAL MASTECTOMY

IO YEAR SURVIVAL RATES

30% internal mammary+	S54% NED 55.5% survival 7.3% local recurrence
47% axilla+	{ 55.5% survival
54% lymph nodes+	[7.3% local recurrence

Lymph Nodes	No. of Patients	NED	Survival
All clear Only axilla+ Only internal	144 73 23	72% 53% 52%	75 % 53 % 52 %
mammary+ Both axilla and internal mam-	75	20%	21 %
mary+			
Total*	315	54%	55.5%

<sup>\* 26 (8%)</sup> developed a new cancer in opposite breast—11 NED 10 years after first operation.

 $a_3$  (7%) died of other causes—clinically free of breast cancer. NED=no evidence of disease.

in these lymph nodes diminishes the prognosis of the individual patient. Detailed study of 5 year salvage data on 500 patients treated by the extended procedure shows that the 5 year salvage rate is uniformly lower in each sector with or without axillary disease when the internal mammary lymph nodes contain metastatic cancer (Table VII). We believe that lymph node involvement is directly related to the general progression of disease. As the number of lymph nodes or the number of lymph node areas affected with metastases increases, concomitant spread of disease through lymphatics and blood vessels and development of systemic metastases also increases. There is general agreement that the greater the extent of disease in the breast and in the primary lymph nodes draining the breast, the poorer is the prognosis for the patient. Review of 148 patients (Table VIII) treated by the extended radical mastectomy, who had positive internal mammary lymph nodes, bears this theory out-but only to a degree! Although the best salvage following the extended operation was attained in patients with only I internal mammary lymph node involved, a good number of patients with 3 or more internal mammary lymph nodes involved were salvaged at 5 years. Four of 7 patients with 3 or more internal mammary lymph nodes involved with metastases were free of disease 5 years following surgery when the axillary lymph nodes were clear, and 35 per cent were free of disease when the axillary lymph nodes contained metastatic cancer. Another surprising finding was the fact that the presence of positive internal mammary lymph nodes in the first interspace level did not result in a catastrophically poor salvage rate. As a matter of fact, 75 per cent of patients with involved lymph nodes in the first interspace were free of disease at 5 years when the axilla was clear and 30 per cent were free of disease when the axilla was involved with disease. Although the addition of supervoltage radiation therapy did not appear to affect the salvage rate or the incidence of local recurrence in 148 patients with positive internal mammary lymph nodes, these data may be misleading (Table IX). In

TABLE VII

EXTENDED RADICAL MASTECTOMY

500 Consecutive Cases

1952-1964

	Axilla	5 Year salvage, clinical free of disease			
Sector	lymph nodes	No. of patients	%		nammary nodes
				Neg. (%)	Pos. (%)
A	   	103 41	75 58	79 67	46 52
В	- +	100 88	78 48	81 51	46 43
С	_ +	19	63 58	77 75	33 45
D	  -  +	28 30	79 60	80 84	66 41
E	<del>-</del>	7 33	85 48	80 60	100 (2) 31
F	- +	5 20	100 65	100 82	44
G	- +	2 5	1∞ 20	100 33	0

general, the patients who did not receive supplementary cobalt 60 therapy had more localized disease than those receiving treatment. We feel that local control was improved by the addition of supervoltage radiation therapy and that some increase in salvage may have resulted, as well, in the patients with more extensive disease who usually received postoperative radiation therapy. Seven per cent of all patients included in the 500 being analyzed for 5 year salvage developed local recurrence in the treated field: one-half as the first sign of recurrence and the remaining half following the appearance of systemic disease.

Many factors affect the prognosis of the patients with breast cancer, such as stage of disease, grade of tumor and resistance of the host, to name a few. At present, of necessity, we are limited to a local attack in our primary curative treatment. All of us desire to enhance the immune resistance of the host, but we know very little concerning the mechanism for achieving such an ideal. Although BCG injections are being given in an attempt to stimulate a nonspecific immune response, there is no evidence that this has influenced the course

TABLE VIII

EXTENDED RADICAL MASTECTOMY
5 Year Salvage of 148 Patients with Positive Internal
Mammary Lymph Nodes

No. of Involved Lymph Nodes	No. of Patients	5 Years Alive (%)	5 Years NED (%)
1	66	59	52
Axilla—	19	68	58
Axilla+	47	55	49
2	35	54	43
Axilla —	10	50	40
Axilla +	25	56	44
3 or more	47	55	38
Axilla—	7	71	57
Axilla+	40	53	35
+Lymph node 1st interspace Axilla - Axilla+	70 12 58	54 75 50	37 75 30

NED=no evidence of disease.

TABLE IX
EXTENDED RADICAL MASTECTOMY
Radiation Therapy to 148 Patients with Positive
Internal Mammary Lymph Nodes

	Total Patients	No Radia- tion	Radia- tion
No. of patients	148	45	103
5 years alive	84 57%	60%	55%
5 years NED	64 43%	49%	41%
Local recurrence	24 16%	16%	17%

NED= No evidence of disease.

of breast cancer. Some maintain that less complete operative procedures increase the salvage of breast cancer patients by preserving the immune factor in the regional lymph nodes, others<sup>5</sup> deny this. Others<sup>4</sup> maintain that the extent of the operation has no bearing on salvage. We attempted to compare the relative effectiveness of radical mastectomy versus the extended radical mastectomy procedure. Table x includes a comparison of 5 year salvage rates for 2 asynchronous series treated by radical mastectomy and I treated by the extended operative procedure. It is striking to note that the salvage rate for the 2 radical mastectomy series—one covering the period from 1940 to 1945 and the other including the more recent national adjuvant series from 1957 to 1962—shows no difference for inner and outer quadrant lesions with negative or positive axillary lymp nodes, as demonstrated in the lower two horizontal boxes. In both radical mastectomy series, there is a slightly better salvage for outer quadrant lesions when the axillary lymph nodes are negative, while the salvage rate for the positive axillary lymph nodes remains constant for both inner and outer quadrants—33 to 34 per cent. The extended radical mastectomy procedure resulted in a marked improvement in 5 year salvage clinically free of disease for all patients with axillary lymph node metastases—53 per cent 5 year salvage as compared with only 33 per cent for the classical radical mastectomy procedure. This may be explained by the fact that 52 per cent of all patients with axillary lymph node metas-

Table X
series comparison

	Radical m	Extended	
	Memorial Control Series (1,000) 1940-45	National Adjuvant Series (1,∞5) 1957–∞	Radical Mastec- tomy (500) 1952-64
Axilla+	63	50	47
Inner	57	47	45
Outer	68	54	78
5-year NED	49	56	65
Inner	49	56	65
Outer	48	57	65
NED axilla—	76	80	77
Inner	71	77	76
Outer	82	81	1∞ (7)
NED axilla+	32	34	53
Inner	33	30	51
Outer	32	37	65

tases in this series had internal mammary lymph node metastases as well. Furthermore, the patients included in the extended radical mastectomy series contained a disproportionately high number of patients with primary tumors arising in the parasternal sectors (A and C) with an extremely high incidence of internal mammary lymph node metastases. Despite this, the 5 year salvage rate for patients with negative axillae treated by the extended radical procedure is equal to or better than that attained in the radical mastectomy groups. A definite advantage is demonstrated when the more complete operative procedure is applied to patients with a high risk of internal mammary lymph node metastases.

No convincing evidence has been presented which would indicate that any less adequate local treatment of breast cancer, which is more apt to leave residual tumor undisturbed in the primary site, has improved the salvage of this disease. In the few articles which infer that such an event has occurred, the improvement cannot be attributed to the less adequate surgical procedure but rather to the more careful selec-

tion of optimal patients with more localized disease.

#### SUMMARY

Aggressive primary therapy—surgery combined with irradiation—which is designed to treat the entire breast as well as both primary lymphatic depots of the breast has resulted in marked improvement in local control and has increased over-all salvage as well.

Primary breast cancers which have already spread to the internal mammary lymph nodes can be salvaged long-term wise through aggressive surgery and radiation therapy.

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# ADJUVANT CHEMOTHERAPY IN THE RADICAL TREATMENT OF CARCINOMA OF THE BREAST—A CLINICAL TRIAL\*

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DURING the last 30 to 40 years the radical treatment of carcinoma of the breast has been based broadly on the 2 established modalities, surgery and radiation therapy. Various authors have stressed the exact role of each of the 2 classical modalities with opinions differing widely as to the importance of either. As a result the over-all picture is confused with no agreement as to which combination can be considered the most efficient, *i.e.*, that which will result in the highest survival rate, malignancy free at 5 years.

The methods advocated range from: (1) radical surgery with heavy postoperative irradiation as suggested by Urban<sup>11,12</sup> and Engelstad<sup>2</sup>; (2) careful case selection with no postoperative irradiation as outlined by Haagensen<sup>8,4</sup>; and (3) conservative surgery and heavy postoperative irradiation as practiced by McWhirter<sup>7</sup> and Mustakallio.<sup>8</sup>

Even the operability rate varies enormously in different institutions and figures varying from 23-80 per cent are quoted in the world literature. No clear-cut answer is, therefore, available as to which of the several approaches is that of choice, or even if true differences in survival occur.

Improvement in surgical supportive measures, and radiation therapy technologic advances in the last 25 years have not produced the expected large increase in survival. Such improvements that have occurred have been marginal, as shown in Table 1.

It would appear, therefore, that the maximum survival rate possible has now been reached by this combined surgical—radio-therapeutic approach, and an alternative or additional modality would have to be employed to raise the survival rate further.

With the rapid development of chemotherapy in the treatment of malignant disease, the use of such an agent seemed an appropriate avenue to explore. Numerous chemotherapeutic agents have been found to be effective, especially in the control of lymphomata or reticulosis, although the chemosensitivity of the "solid" tumors, with the sole exception of Wilms' tumor and chorion epithelioma, has on the whole been disappointing.

The work of Long et al.<sup>5</sup> and Roberts and Cole<sup>9</sup> appeared to demonstrate irrefutably the presence of the circulating cancer cell in the peripheral blood, and further showed a quantitative correlation between the extent of the malignancy and the circulating cell count; a rise in count associated with manipulative procedures of the primary tumor and a decrease in cell count when the appropriate chemotherapeutic agent was given systemically. The latter finding appeared at last to be the nearest approach to a chemotherapeutic-malignancy-sensitivity test analogous to antibiotic sensitivity and bacteriologic work. Although this work

Table I
5 YEAR SURVIVAL—MALIGNANCY FREE:
COMPARISON OF RESULTS OVER
20 YEAR PERIOD

(Stages I and II-Operable)

	Per Cent 5 Year Malignancy Free	
Engelstad <sup>2</sup>	64	
McWhirter7	58	
Haagensen <sup>8,4</sup>	59	
Manchester <sup>10</sup>	56	

<sup>\*</sup> From the Department of Radiotherapy, Newcastle General Hospital, Newcastle upon Tyne, England.

was subsequently disproved, it seemed logical that many viable tumor cells do seed through the blood stream and become the foci of subsequent metastases. Furthermore, the administration of a chemotherapeutic agent could affect both the primary tumor as well as the viability and quantity of these circulating cells. This, together with the aforementioned proven effectivity of chemotherapy in the management of Wilm's tumor and chorion epithelioma, suggested that a chemotherapeutic agent as an added modality to surgery and radiotherapy in the radical treatment of carcinoma of the breast might be instrumental in effectively raising the survival rates.

There has been recent interest and thought veering towards the part that the body defences have to play in the control of malignancy of carcinoma of the breast. It has been suggested that absence of natural immunity protection leads to the development of distant metastases, and that accepted treatment methods now employed may, in fact, lead to a fall in survival rate by a breakdown of this immunity mechanism. Bond<sup>1</sup> suggests, therefore, that "castration, chemotherapy, corticoids and radiation are best deferred until metastatic disease is active, the disease is uncontrollable and immunity protection has broken down," and that management of the primary tumor should be by "gentle local mastectomy." Furthermore "there is no place in the early stages for ill chosen chemotherapy only 5 fluorouracil appearing to be safe, being the only nonlymphopenic agent."

It was felt, however, that a trial should be attempted to investigate the effectivity of a chemotherapeutic agent used as an adjuvant to surgery and radiotherapy in operable cases of carcinoma of the breast.

In conjunction, therefore, with the Department of Surgery at the Newcastle General Hospital it was felt that a randomized trial should be undertaken in which 2 groups of cases were to be compared.

Group I. Those cases treated in the pre-

viously routine manner of surgery with postoperative irradiation.

Group II. Cases treated by surgery and radiation therapy with the addition of pre- and postoperative chemotherapy.

In this way the number of variants in the treatment plan was kept to a minimum, *i.e.*, the presence or absence of chemotherapy. Cyclophosphamide was chosen as the chemotherapeutic agent, being of a relatively mildly toxic nature as judged by the known depression on the bone marrow following systemic use.

The surgical procedure was not limited to one type of operation, either a simple or radical mastectomy being undertaken dependent on the site and size of the primary tumor. In the majority of cases, however, a simple mastectomy was the operation employed in both groups.

### TECHNIQUE

Cases were included of carcinoma of the breast Stage I and Stage II Steinthall classification, i.e., confined to breast and/or axilla, in good general condition and under the age of 70 years. Full routine investigational procedures were carried out prior to hospital admission. Cyclophosphamide was administered on hospitalization by daily intravenous injection at a dose of 2-3 mg./kg./body weight. The preoperative chemotherapy was commenced 4 days prior to surgery, a fifth injection was given on the day of the operation and for 5 days postoperatively. A full blood study was undertaken every other day during the patient's stay in hospital and subsequently at weekly intervals. Details of the condition of the wound were noted and delays in wound healing recorded. Subsequently, radiotherapy was administered, dependent on wound healing, using a high energy cobalt 60 machine by a constant plan of application and dosage with daily fractionation and a 3 field distribution. The degree and extent of the reaction were

noted in detail with length of time the reaction lasted.

Routine follow-up was then proceeded with in the usual way.

#### RESULTS OF TRIAL

#### WOUND HEALING

There were no adverse effects noted on wound healing. The rate and time of healing being almost identical in both groups, as shown in Table II.

Hematoma and seratoma occurred in about 10 per cent of cases in both groups, and wound infection was similarly negligible.

#### REACTIONS

The enhancement of skin reactions by the combination of actinomycin D and irradiation in the treatment of Wilms' tumor is well known. In this series no evidence of reaction potentiation was demonstrated. The reactions were classified as:

2nd degree signifying dry desquamation and

3rd degree—signifying moist desquamation or vesication.

Analysis showed a similar distribution and degree of reactions in both groups (Table III).

#### EFFECT ON BLOOD CELL COUNT

Cyclophosphamide, being a potent cytotoxic agent in common with other alkylating agents, could be expected to have toxic effects on the bone marrow.

Leukopenia and thrombocytopenia are foreseeable effects and could have been a limiting factor in the continued use of this agent. In this series the effects, as expected from previous experience, could be classified as mild. Less than one-quarter of the

Table II

comparison of wound healing times

(weeks)

Chemotherapy	AV 2.5	Mean 2
Control	AV 2.8	Mean 2

AV = average.

TABLE III
COMPARISON OF REACTIONS

	Degree	No. of Patients
Chemotherapy	2nd 3rd	15 28
Control	2nd 3rd	11 29

2nd degree = dry desquamation. 3rd degree = moist desquamation.

cases had a fall in white blood cell count below the 2,000/cu. mm. mark and in these the initial count was not unduly low; in retrospect, this leukopenia could not have been forecast at the outset. It was found that the fall in white blood cell count was almost entirely due to the polymorphonuclear depression, and the absolute lymphocyte and platelet count falls were minimal. In most cases the blood cell count had returned to pretreatment levels within 1 month of cessation of chemotherapy but in those cases with lower blood cell counts, as might be expected, the return to initial level was delayed up to 4 weeks later.

### ALOPECIA

Epilation occurred in 20 per cent of cases in the chemotherapy group. This was usually complete. In most cases regrowth of hair was complete in 3 to 6 months but not always of the same color, texture or quality.

#### GENERAL UPSET

General upset in the form of nausea, anorexia, etc., was minimal and chemotherapy cystitis was not noted.

#### EFFECTS ON MALIGNANCY

Survey of the over-all or crude survival at a minimum of 3 years following treatment shows that those cases treated with chemotherapy in addition to surgery and irradiation fare appreciably worse than those without this added modality. This

TABLE IV
CRUDE 3 YEAR SURVIVAL FIGURES

	Chemo- therapy	Control	
Alive and cancer free	18	25	
Dead or recurrent	25	15	

difference in survival is on the borderline of being highly significant statistically (Table IV).

Analyzed in greater detail, according to the extent or stage of the malignancy, the survival figures for each stage are shown in Tables v and vi.

It is evident that the above differences between the 2 groups are due almost entirely to the decrease in survival in the Stage II or more advanced tumors, that is, in cases already with established metastases.

Analysis of the sites of metastases at the time of death shows a considerable increased incidence in both generalized and bone secondary metastases in the chemotherapy group, suggesting an enhancement of blood stream dissemination for this group of cases (Table VII).

It can be assumed, therefore, that the addition of the chemotherapeutic agent has not prevented the establishment of systemic metastases in the Stage II cases where the numbers of metastasizing viable cells can be assumed to be greater.

CONCLUSIONS

It can be concluded from the trial that:

Table V
3 YEAR SURVIVAL-CONTROL GROUP
(control—number 40)

***************************************		
Alive	Stage I Stage II	15 10
Dead	Stage I Stage II	5 8
Alive (rec.)	Stage I Stage II	I I

TABLE VI
3 YEAR SURVIVAL—CHEMOTHERAPY GROUP
(cyclophosphamide—number 43)

Alive	Stage I	16
	Stage II	2
Dead	Stage I Stage II	5 17
Alive (rec.)	Stage I Stage II	I 2

(1) in the survival of operable cases of carcinoma of the breast treated by this combination of surgery, irradiation and the chemotherapeutic agent cyclophosphamide, the results at a minimum of 3 years postoperatively are considerably worse than a similar group treated with surgery and irradiation only; and (2) the chemotherapy has failed, principally in the more advanced cases, and, furthermore, the increase in generalized and bone secondary metastases in the chemotherapy group, presumably due to blood stream dissemination, indicates that this failure occurred in the very cases where it was hoped that some degree of control would be effected.

The differences between the 2 groups are found to be on the borderline of high significance statistically and would appear to lend support to the thesis that "there is no place in the early stages for ill chosen chemotherapy" despite the absence of lymphopenia.

#### SUMMARY

A report is presented of a randomized clinical trial to investigate the effects of

Table VII

SITES OF METASTASES—BOTH GROUPS

(per cent deaths)

	Chemotherapy	Control
Generalized	54	43
Chest	17	15
Bone	20	7
Coincident	7	35

adding a chemotherapeutic agent, i.e., cyclophosphamide, to the routine modalities of surgery and radiation therapy in the radical treatment of operable carcinomata of the breast.

The rationale, protocol and method are outlined and the results shown. Assessment of both immediate as well as longer term effects on malignancy is made.

No undue side effects are noted but the malignancy control in the group given chemotherapy at a minimum of 3 years postoperatively is appreciably worse than in the group not given this agent.

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# DISTANT METASTASES AS AN EVALUATION OF THE TREATMENT OF BREAST CANCER\*

By F. M. NICHINI, M.D., and K. C. TSIEN, M.A. PHILADELPHIA, PENNSYLVANIA

DURING the period 1940–1969, 1,055 postmastectomy patients with carcinoma of the breast were seen in the Radiotherapy Department of Temple University Hospital. In the present report only 3 categories will be discussed (Table I, Categories A, B and C).

#### MATERIAL AND METHOD

Patients in Category A are confined to the period 1956–1963 in contradistinction to the other 2 categories which are taken from the whole 29 year period under study. The eventual aim is to extend Category A to encompass the whole series, but because of the stringent requirements necessary for inclusion in this group, only the period 1956–1963 has been covered for this preliminary report.

All the cases in this study were clinically Stage I or II breast cancers treated by radical mastectomy and postoperative irradiation to the lymph node drainage areas. In order to be included in Category A, clinical manifestation of metastases had to be confirmed by biopsy, roentgenography or autopsy. It was mandatory that the death of the patient be due to the direct effect of hematogeneous metastatic disease. Deaths from unrelated causes, despite the presence of hematogeneous metastases, were excluded from this category as were all cases in which a second primary malignancy of any form was diagnosed during life or discovered at postmortem examination. Sixty-nine patients are included in

Category B consists of 64 cases taken from the whole series who are to date still alive without any evidence of active dis-

Table I

CASES OF POSTMASTECTOMY PATIENTS SEEN IN
RADIOTHERAPY DEPARTMENT OF TEMPLE
UNIVERSITY HOSPITAL 1940–1969

	No.	
A.	Patients dead from bloodborne meta- stases	69
В.	Patients now living free from disease for a minimum of 5 years up to last follow-up examination (January 1970)	64
C.	Patients living with metastases up to last follow-up examination (January 1970)	7
D.	Patients dead from disease and other causes (January 1970)	727
E.	Lost to follow-up	134
F.	Consultation only	54
	Total	1,055

ease, either in the form of regional recurrence or bloodborne metastases. Only cases seen up to December, 1964 and still alive and disease free are included.

The 7 cases in Category C are alive, but have proven bloodborne metastases.

The survival curve for patients in Category A (Fig. 1) shows a 31.5 per cent 5 year survival which is comparable to other published data for a similar group. The interval, within this group, from mastectomy to the development of manifestation of metastases shows that over 80 per cent of patients developed metastases within 5 years of their mastectomies (Fig. 2). This observation also compares favorably with

<sup>\*</sup> Presented at the Fifty-second Annual Meeting of the American Radium Society, Coronado Island, San Diego, California, March 1-5, 1970.

From the Temple University Hospital, Philadelphia, Pennsylvania.

Cutler et al.'s much larger series<sup>5</sup> in which 80.3 per cent had developed metastases by 5 years (Table 11).

With the development of bloodborne metastases, roughly 75 per cent of the patients died within 2 years and practically all had succumbed within 5 years of their manifestation (Fig. 3).

The reason for dividing the material into 3 categories is to facilitate analysis of pertinent prognostic factors that might be observed. Was there, as it were, a difference between Category A and B that could have been identified at the onset of the disease and which could have helped determine the likely outcome?

Apart from a few patients on protocol study the bulk of the patients referred to the department for postmastectomy irradiation had positive ipsilateral axillary lymph node involvement. Patients with outer quadrant lesions without axillary lymph node metastases were not irradiated. Medial quadrant lesions with negative ipsilateral axillary lymph nodes did receive postoperative irradiation.

#### RESULTS

### LYMPH NODE INVOLVEMENT

In the analysis of the significance of lymph node involvement, only outer quadrant or central primary lesions are included since the data from medial quadrant lesions would have a different significance

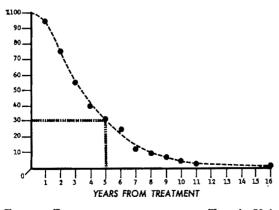


Fig. 1. Breast cancer cases seen at Temple University Hospital with bloodborne metastases: per cent survival.

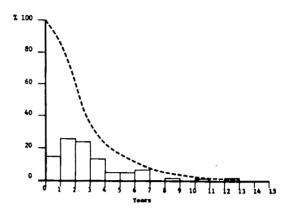


Fig. 2. Per cent of patients versus time interval from mastectomy to development of manifestation of metastases.

when attempting to correlate the prognostic value of axillary lymph node involvement. Metastases beyond the breast to the internal mammary chain can, for example, occur with a medial quadrant lesion without ipsilateral axillary lymph node metastases.

There appears to be little evidence to support the view that minimal axillary lymph node involvement is suggestive of a better prognosis; 6.7.8 indeed the striking feature is that massive axillary lymph node metastases denote no worse prognosis than

Table II
INTERVAL FROM PRIMARY TREATMENT TO THE
MANIFESTATION OF METASTASES

	Temple University Hospital Data 1970		Cutler <i>et al.</i> Data* 1969		
	No. of Pa- tients		Cent	No. of Pa- tients	Per Cent
12 mo. 12-23 mo. 24-35 mo. 36-47 mo. 48-59 mo. 5-9 yr. 10+ yr.	9 16 15 8 3 8	14.8 26.2 24.6 13.1 4.9 13.1 3.2	83.6	184 181 105 79 49 103	24.7 24.3 14.1 10.6 6.6 13.8 5.9
Total	61			745	

<sup>\*</sup> Interval from diagnosis of breast cancer to diagnosis of disseminated disease.

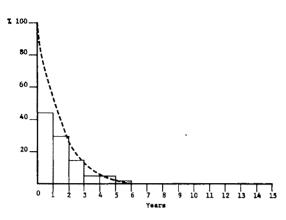


Fig. 3. Per cent of patients versus time from manifestation of metastases to death.

2 or less positive lymph nodes in the Category A cases (Table III).

This trend is further supported by the figures for the category B group where in the case of the still surviving patients a greater proportion of those with more extensive lymph node disease have out-lived the group with involvement of 2 lymph nodes or less (Table IV).

## TUMOR GRADE

These 2 categories, A and B, are comparable in terms of clinical stage of the disease, age, location of the primary tumor and treatment. They differ considerably however, with regard to the histologic grading of their primary tumors. In the dead group, 26 out of the 35 were Grade III tumors, whereas only 2 of the 25 living patients had primary tumors of this grade.

TABLE III

AXILLARY LYMPH NODE INVOLVEMENT IN PATIENTS
DEAD FROM BLOODBORNE METASTASES

No. of	Dead Within Period Shown				
Lymph Nodes	1-5 yr.	6–10 yr.	II yr. and over		
2 or less 14		5	I		
3-4	6	warmood	photograph (		
5 or over	13	5	2		

TABLE IV

AXILLARY LYMPH NODE INVOLVEMENT
IN LIVING PATIENTS

No. of Lymph Nodes	Patients Presently Alive and Cancer Free		
Lympit Nodes	5–9 yr.	10 yr. and over	
2 or less	8	5	
3-4	6	7	
5 or more	8	10	

The numbers in these groups are small, but it would appear that a greater proportion of those still living who had 5 or more involved axillary lymph nodes had Grade 1 or 11 primary tumors.

A significant correlation exists between the grade of the primary tumor and the occurrence of bloodborne metastases. Of the 46 patients with Grade III primary tumors, 39 had metastasized within 5 years of their mastectomies. Only 10 of 38 cases with Grade I or II tumors had metastasized within the same time period (Table v).

#### MENOPAUSE

Age 50 was taken as the determinant of the menopause; patients 50 years old or younger were considered premenopausal. In every other respect pre- and postmenopausal groups were comparable, even to the actual number in each group as well as to

TABLE V
HISTOLOGIC GRADING

No. of Patients	I and II	III	Total
Free from metastases for 5 years or more*	28	7	35
Metastases developed within 5 years	10	39	49
Total	38	46	84

<sup>\*</sup> Duration from the time of primary treatment (mastectomy). Chi-square with Yates' correction=27. Conclusion: highly significant.

TABLE VI
INFLUENCE OF MENOPAUSE

No. of Patients	Pre- meno- pause	Post- meno- pause	Total
Free from metastases for 5 years or more* Alive, free of	40	35	75
metastases	(35)	(29)	
Alive, now with metastases	(1)	(0)	
Dead, due to metastases	(4)	(6)	
Developed metastases within 5 years* Alive with meta-	27	38	65
stases	(3)	(3)	
Dead, due to metastases	(24)	(35)	
Total	67	73	140

<sup>\*</sup> Duration from the time of primary treatment (mastectomy). Chi-square with Yates' correction = 1.5. Conclusion: not significant.

the relative numbers that developed metastases within 5 years (Table VI).

Theinfluence of tumor grade on survival is seen in Table VII, a comparison in which 40 of the 55 patients who died had Grade III tumors, whereas only 4 of the 28 living patients had tumors of this grade.

TABLE VII
TUMOR GRADE COMPARISON IN PRE- AND
POSTMENOPAUSAL GROUPS

Category	Dead From Metastases		Living Cancer Free	
Tumor Grade	I and II	III	I and II	III
Premenopausal group 17 Grade I and II 18 Grade III	5	17	12	I
Postmenopausal group 22 Grade I and II 26 Grade III	IO	23	12	3
Total	15	.40	24	4

TABLE VIII
PREMENOPAUSAL GROUP

	Castra- tion*	No Cas- tration	Total
Free from metastases for 5 years or more	20	20	40
Metastases developed within 5 years	9	3	12
Total	29	23	52

<sup>\*</sup> Castration at the time of mastectomy.

A comparison of 20 patients castrated at the time of their mastectomies with 20 premenopausal women not castrated at the time of mastectomy shows that the latter were not adversely affected by foregoing ovarian ablation (Table VIII).

The patients castrated at the time of manifestation of metastases had a greater over-all survival time from mastectomy to death than those who underwent castration at the time of mastectomy, as well as a more prolonged interval between the manifestation of metastases and death (Table IX).

#### DISCUSSION

Assessment of the premenopausal group is difficult because of the small number of cases available. Some observations may

Table IX
SURVIVAL FOLLOWING CASTRATION

	Mean Survival in Months		
	Mastec- tomy to Meta- stases	Metas- tases to Death	Mastec- tomy to Death
Castration at time of mastectomy (7)	16	5	21
Castration at manifestation of metastases (16)	36	20	56

however be made. The occurrence of metastases within 5 years in those that underwent prophylactic castration may reflect a high proportion with occult metastases at the time of castration, or a lack of control of the progression of established metastases by this procedure, or a combination of both factors. There certainly was not an overwhelming number of patients developing metastases in the group that was not subjected to ovarian ablation at the time of mastectomy. It would appear that prophylactic castration is no guarantee for tumor control, and since effective palliation with prolongation of life occurred in those receiving therapeutic castration, the latter procedure is to be preferred. All the castrations in this series were by surgical ablation.

In this study, to date, the number of involved lymph nodes per se, does not appear prognostically significant. It may well be that the number of lymph nodes should be considered with respect to the tumor grade, since this may be taken as an index of the propensity of the tumor to produce hematogeneous metastases and to invade the regional lymph nodes. In those cases where lymphatic invasion is well advanced, but bloodborne metastases occur late, a large number of axillary lymph node metastases would be expected with corresponding good prognosis.

There is no doubt that the tumor grade<sup>1-4</sup> is the most significant prognostic index in this study. It represents a spectrum of tumor characteristics by which the pathologist can classify a tumor by giving it a Grade usually between 1 and 1v. It would seem logical to divide the grades merely into 2 main groups: those with the favorable characteristics and those with the unfavorable ones, thus doing away with the intermediate groups in an attempt to reduce confusion.

In the assessment of the cases in Category A the interval between mastectomy and the manifestation of metastases was compared to the length of survival subsequent to the manifestation of bloodborne metastases.

The tumor free period from mastectomy to the manifestation of metastases was called f, and the period from metastases to death, t. The ratio t/f was called the Prognosis Factor.

This factor may be expressed by the equation:

Prognosis Factor = 
$$\frac{t}{f} = \frac{1}{f} F(f, x, y, z)$$
,

where x, y, z represent various prognostic factors such as tumor grade, number of involved axillary lymph nodes, etc.

Currently in progress is a study to ascertain the relative values of the various prognostic factors involved by substituting x, y, z, by data from the present series.

#### CONCLUSION

In the reported series 497 patients died from their breast cancer despite the fact that they all had clinically Stage I or II lesions treated by radical mastectomy. Even though this series is biased towards cases with axillary lymph node disease (hence the referral to a radiotherapy department), the primary treatment was effective in controlling the regional aspect of the disease, but was grossly inadequate in the over-all control of the patient's malignancy.

Present therapy for operable breast cancer fails to take into account the large number of patients who have already developed occult bloodborne metastases. Efforts should be directed to the establishment of more effective methods of identifying occult hematogeneous metastases prior to surgery. The recognition of the patient with occult disseminated disease would be the most effective prognostic index available. Until this goal can be achieved, the value of tumor grading should not be ignored.

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# THE USE OF THERMOGRAPHY IN DETECTION OF METASTATIC BREAST CANCER\*

By CORINNE FARRELL, M.D., JOHN D. WALLACE, A.B., and CARL M. MANSFIELD, M.D.

PHILADELPHIA, PENNSYLVANIA

A THERMOGRAM is a graphic display of infrared emission from a body made by a scanning device.

Total body thermography is a technique that has been used at Thomas Jefferson University Hospital during the past 4 years. Preliminary study indicates that this technique of total body thermography can be an aid in determining the presence of recurrence and metastases of primary breast carcinoma, as well as the recurrence of a second malignancy. It may also be an aid in distinguishing benign and malignant disease.

This paper presents the evaluation of thermography in 126 patients with known carcinoma of the breast.

We use the Smith-Pyroscan, which is a high speed infrared scanner that gives a paper record for interpretation. The polarity of our studies has been selected so that the warmer areas are recorded darker than the colder areas. This polarity reversal has tended to increase the accuracy of interpretation. 1–6

#### PROCEDURE

After removing all clothing, the patient is exposed for 10 to 12 minutes in an examining room where the ambient temperature has been stabilized to 68°F. The entire surface of the body is then scanned in the anterior, posterior and both lateral projections. Our scanning device is capable of examining a 24×24 inch area in 30 seconds making 40,000 separate temperature measurements. Because of the small area scanned, the body is done in segments. Details of instrumentation, procedure and in-

terpretation have been documented elsewhere. 1-5

#### RESULTS

The scans were read without prior knowledge of the patient's clinical status. The medical and radiation therapy records, roentgenograms, nuclear medicine studies, and pathologic material were reviewed approximately 6 months after the study. Six hundred and eighty-two areas of interest were studied; 378 of these areas were thermographically negative and were confirmed as such by conventional diagnostic techniques; 211 areas of interest were read as positive by thermography (Table 1). These latter areas were confirmed by conventional techniques: 98 by roentgen examination, 53 by pathology, surgery or autopsy microscopic findings; 17 by nuclear medicine studies; and 43 by physical examination. Of interest are 7 findings originally considered false positive because of the negative conventional diagnostic studies. In 3 to 6 months additional roentgen studies were positive. In these instances, the thermogram had detected the lesion prior to

Table I

RESULTS IN 126 BREAST CANCER PATIENTS

Results by	Results by conventional technique		
thermography	Negative	Positive	Total
Negative Positive	378 72	21 211	399 283
Total	450	232	682

<sup>\*</sup> Presented at the Fifty-second Annual Meeting of the American Radium Society, Coronado Island, San Diego, California, March I-5, 1070.

From the Department of Radiology, Thomas Jefferson University, Philadelphia, Pennsylvania Supported in part by PHS Training Grant from NCL and Public Health Service Grant 5-TOI-CA-5109.

TABLE II
SUMMARY OF THERMOGRAPHIC FINDINGS IN PATIENTS

	No.	Per Cent
Confirmed thermographic findings	589	87
False positive findings	72	IO
False negative findings	21	.3

other studies. Seventy-two suspected areas were not proven abnormal by conventional techniques, giving a false positive rate of approximately 10 per cent.

The false negative rate in this series was 3 per cent. There were 21 areas of pathology proven by conventional techniques to have pathology, but reported as having negative thermographic findings. A review of the thermography examinations failed to reveal the presence of thermographic abnormality (Table II).

In the areas where conventional techniques indicated no pathology, the thermogram was read as positive 25–30 per cent of the time. This high false positive figure may have been due to 2 factors: initial inexperience of the reader in the interpretation of total body studies; and the early

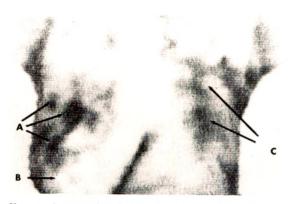


Fig. 1. An anterior thorax thermogram of a 58 year old female showing an increase in temperature of a second primary carcinoma of the breast (A); the nipple (B). The increased temperature areas outlined by the arrows (C) were interpreted and confirmed as palisading vessels in the previous left mastectomy scar. Biopsy and radical mastectomy confirmed adenocarcinoma of the right breast, 5 years following the same procedure for adenocarcinoma of the left breast.

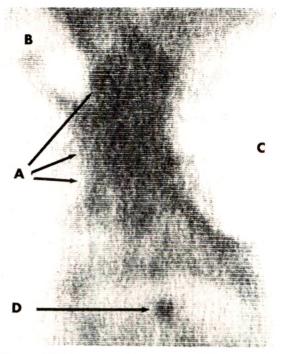


Fig. 2. Thermogram of a 51 year old female with histologic proof of recurrence in the operative site 1½ years following radical mastectomy for adenocarcinoma of the right breast. The area of increased temperature outlined by arrows (A) is a recurrence in the skin of the right breast and skin overlying the sternum. Other structures are: (B) right axilla; (C) left breast; and (D) umbilicus.

high index of suspicion of the referred radiation therapy patients. It is our impression that the false positive examination rate has been reduced as the study has progressed.

In the prebiopsy or pretreatment patient evaluation, thermography of the breast has been used as a clinical modality at this institution since 1966 and has proven to be a sensitive detection technique, especially with early primary lesions.<sup>1,5,7</sup>

Occurrence of a second primary lesion is possible in patients with this disease, so that the use of this technique at follow-up intervals is rewarding. The thermogram in Figure I demonstrates an area of increased temperature in the right breast. Biopsy and radical mastectomy gave microscopic proof of a second adenocarcinoma of the breast. The left breast had been removed 5 years previous to this examination.

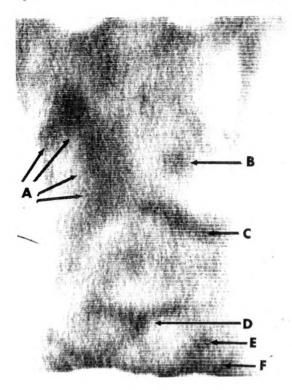


Fig. 3. The anterior trunk thermogram shows areas of increased temperature in the region of the mastectomy scar, skin in operative area, and a metastatic lateral edge of the sternum (A) and left breast (B). Biopsy of skin areas and roent-genograms of the sternum confirmed recurrence and metastasis of adenocarcinoma of the breast. This 41 year old female underwent radical mastectomy and postoperative radiation therapy 8 months prior to this study. Other structures include: (C) opposing skin surfaces of anterior chest and breast; (D) umbilicus; (E) left lateral edge of Pfannenstiel's crease and (F) inguinal crease.

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Recurrence of a primary breast carcinoma is frequently found. In Figure 2, the area of large increased temperature seen on this anterior thorax thermogram was his-

tologically proven to be recurrence of an adenocarcinoma of the breast. The breast had been amputated 1½ years previous to this study. Metastatic bone disease occurs frequently in this neoplasm. In Figure 3 the thermogram shows increased temperature in the right side of the sternum. Roentgenograms confirmed the presence of a bone metastasis.

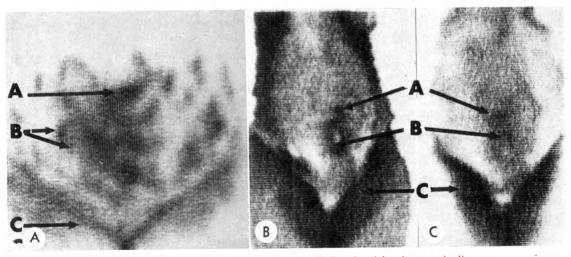


Fig. 4. (A) Anterior thermogram of the pelvis of a 55 year old female with microscopically proven carcinoma of the breast metastatic to the ovary. The area of increased heat in the mid pelvis is thought to represent metastatic disease to the ovary and peritoneum. (A) Umbilicus; (B) metastatic disease of the ovary and peritoneum; (C) inguinal fold. (B and C) Anterior thermograms of the pelvis 3 weeks and 6 weeks following beginning of chemotherapy.

Carcinoma of the breast can metastasize to the ovary. In Figure 4.1 the thermographic study of the abdomen shows a very large area of increased temperature in the pelvis. Exploratory laparotomy confirmed the diagnosis of metastatic breast disease to the ovary. Follow-up examinations at 3 and 6 week intervals (Fig. 4, B and C) demonstrate decrease in the size of the pelvic mass, while the patient underwent chemotherapy.

Liver metastasis has also been found. In

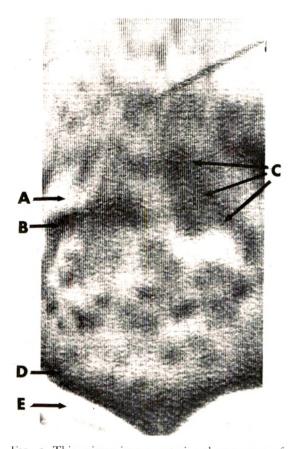


Fig. 5. This mirror image anterior thermogram of the abdomen demonstrates an area of increased temperature in the region of the liver as outlined by arrows (C). Isotope scan confirmed abdominal liver uptake due to metastatic disease. Other structures include: (A) remaining left breast; (B) breast and anterior chest skin apposition; (D) Pfannenstiel's crease and inguinal crease; and (E) patient drape.

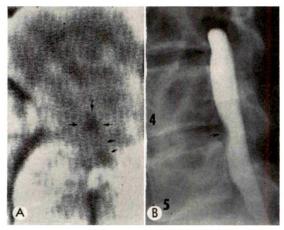


Fig. 6. A 53 year old female with biopsy and radical mastectomy for adenocarcinoma of the left breast. (A) Thermogram of the posterior thoracolumbar region 1 year post mastectomy for carcinoma of the right breast. The area of increased temperature, as outlined by arrows, was thought to be disk disease rather than metastatic disease. (B) The oblique view of the lumbar spine demonstrates the myelographic findings of herniated nucleus pulposus, as marked by arrow. Surgical exploration confirmed the suspicion of disk disease.

Figure 5, the area of increased temperature in the anterior view of this abdomen represents metastatic disease as proven by needle biopsy. The primary was carcinoma of the breast.

The association of benign disease with malignancy is sometimes forgotten, particularly if there is a possibility or probability of metastatic disease. In Figure 6A, the thermogram demonstrates an area of increased temperature in the L3, 4, 5 region, that was thought to represent disk disease in this postmastectomy patient rather than metastatic disease. The myelogram (Fig. 6B) and surgical exploration confirmed the presence of disk disease. The primary was a histologically proven adenocarcinoma of the breast 3 years prior to this examination.

Metastatic pulmonary disease can be detected, but it is difficult to interpret unless mediastinal lymph nodes are involved. Lymph nodes in the axilla have been found,

but it has been our experience that vascular changes after surgery in the lateral scan and the difficulty in cooling this area of the body make interpretation difficult.

#### SUMMARY

Our experience to date has shown that total body thermography can be an aid in the search for metastatic disease in patients with carcinoma of the breast. In our series of 126 patients, we found a true positive rate of 87 per cent, a false negative rate of 3 per cent, and the false positive rate was approximately 10 per cent. Of considerable interest were 7 false positive thermograms which were converted to true positives in 3 to 6 months after the original study.

We have found total body thermography useful in locating the site and extent of a primary lesion, a second carcinoma of the breast or recurrent and metastatic lesions. It has also been an aid in differentiating associated benign disease. This examination is inexpensive, consumes little time, causes no patient discomfort and has the added advantage of no exposure to ionizing radiation. This technique is capable of detecting early manifestations of metastatic disease, but such manifestations of dis-

ease should be confirmed by conventional techniques at this time.

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## AIR AXILLOGRAPHY\*

By DENISE OUIMET-OLIVA, M.D. MONTREAL, QUEBEC, CANADA

RECENTLY, in a panel discussion concerning breast cancer, a group of surgeons reproached the radiologists for having concentrated their efforts on the mammary gland to the exclusion of the axilla. This region is still being examined by inaccurate palpation. There is, of course, lymphography of the upper limb, but this examination, besides being somewhat complicated as a routine examination, does not show some groups of lymph nodes, and a lymph node which is totally invaded by a malignant tumor can be missed. The purpose of this paper is to present a new method of demonstrating axillary lymph nodes: the air axillography.

#### METHOD

The axilla on the affected side is shaved, cleansed and a local intradermic anesthesia is used. A tourniquet is placed at the level of the inferior insertion of the deltoid muscle to prevent air leakage along the arm muscles. Finally, 200–300 cc. of air is injected into the prepared area (Fig. 1). A subcutaneous emphysema is thus produced which, owing to brachial compression, re-

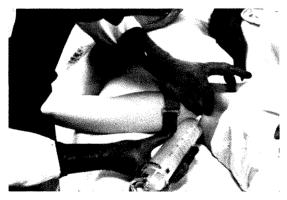


Fig. 1. Air is injected into the axilla under aseptic conditions after an intradermic anesthesia. A tourniquet is applied on the arm.

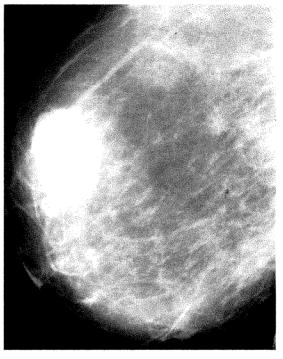


FIG. 2. Mammogram. There is a malignant tumor with irregular contours and hypervascularity (atypical epithelioma).

mains clustered in the axilla and creates a contrast to its contents.

This examination is complementary to mammography. Axillary roentgenograms are taken before and after the air injection. It is recommended that the study be performed bilaterally in order to have a control side as is done in mammography. Tomography may be used also to complete the examination.

#### ADVANTAGES

The study is very simple to perform. The injected air resorbs completely in approximately 2 days. CO<sub>2</sub> or nitrogen protoxide could be used but the handling of these

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Fig. 3. Air axillogram. A 3 cm. lymph node and smaller lymph nodes can be seen which were histologically invaded by carcinoma and clinically undetected in an obese woman.

gases and the manometric verifications complicate the technique.

The time required for the examination is 3–5 minutes.

There is no difficulty in the eventual histologic studies of the axillary lymph nodes.

#### INDICATIONS

This examination is useful in the detection of breast cancer, as it helps to estab-



Fig. 4. Mammogram. There is a central spiculated density; however, no mass was palpated. Ratio of the diameter of vein (RDV)=1.8. (Scirrhous epithelioma.)

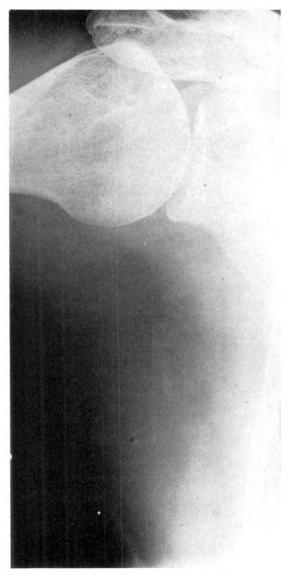


Fig. 5. Air axillogram. A questionable lymph node is seen.

lish the stage of the tumor and thus indicates the treatment regimen. For primary diseases of lymphoid tissue, this technique also may give pertinent information.

### RESULTS

This is a preliminary report, as we have only performed 15 air axillographies to date. Initially, only patients with breast cancers and obvious axillary lymphadenopathies were chosen. Later, examinations



Fig. 6. Air axillogram. A 2 cm. lymph node from the central group was not palpated clinically.

were performed on patients with breast cancer but in whom axillary lymph nodes were not palpable (Fig. 2; and 3). In this last group of patients, enlarged lymph nodes, which were not suspected clinically and which were positive for cancer invasion after removal on microscopic examination, were demonstrated. This situation is encountered particularly in obese patients where palpation of the axilla is difficult (Fig. 4; 5; and 6). Moreover, in a patient without a palpable breast mass and axillary lymph nodes, it was possible to locate both lesions with mammography and air axillography, respectively (Fig. 7, A and B; and 8, A and B). Also discovered with this technique were lymphadenopathies in the axilla opposite a breast cancer. A case of Kleinfelter's syndrome with bilateral gynecomastia and acute mastitis was examined by this method and large axillary lymph nodes were found.

At the present time valid statistics can-

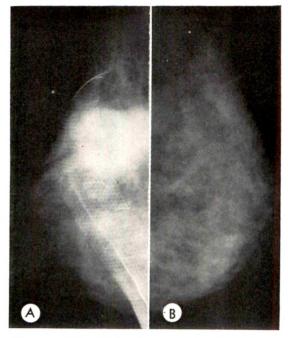


Fig. 7. (A and B) Mammograms. There is a malignant tumor in the upper right breast (A).

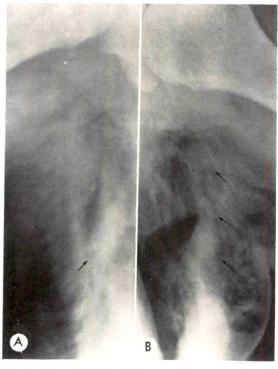


Fig. 8. (A and B) Air axillograms. Numerous lymph nodes in both axillae are seen which were clinically undetectable.

not be given due to the limited number of our cases, but air axillography appears to be an excellent and simple examination which aids in the investigation and helps to decide the treatment regimen in breast cancer and other pathologic processes involving the axillary region.

#### SUMMARY

Injection of air into the axilla is proposed

as a new method for investigating breast malignancies and pathologic processes involving the axilla.

The technique, advantages and a preliminary report are presented.

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# CLINICAL EVALUATION OF TRANSRECTAL PROSTATOGRAPHY\*

By HAJIME SUGIURA, M.D.,† and SUSUMU HASEGAWA, M.D. NAGOYA, JAPAN

SINCE our original report of transrectal approach to the roentgenographic visualization of benign prostatic hypertrophy or hyperplasia, we have continued to utilize this technique in cases of benign hyperplasia, carcinoma, inflammatory disease and normal condition of the prostate. Observations now extend over a 28 month period during which time we employed the procedure in more than 100 patients with satisfactory results and without significant complications.

The purpose of this study is to evaluate the roentgenologic findings in various diseases and the normal condition of the prostate, and to appraise the improved technique. A follow-up report seems justified.

Undoubtedly, the large number of methods developed attests to the imperfection of any one of them, although indirect prostatography has been attempted by many investigators. <sup>2,3,8,9,11,12,16,17</sup> Direct prostatography, on the other hand—injection of contrast material (I or 2 ml. of neoiopax solution) into the prostate gland itself through the urethra with a long McCarthy needle—was introduced by Soifer in 1938. <sup>13</sup> The few investigators who have used this method obtained unsatisfactory results.

Recently it was reported by us that successful visualization of the clear contour of the prostate in benign hyperplasia was done by way of direct puncture of the prostate via the rectal wall, followed by opacification with water soluble contrast material. Reports on such a method have not appeared previously in the literature.

The transrectal approach was chosen in preference to the perineal route, because it is the same as that used for transrectal needle biopsy of the prostate. 1,4-7,10,18

MATERIAL AND IMPROVED TECHNIQUE

During the period from September 1967 to December 1969, a total of 138 transrectal prostatographies have been performed on 121 patients in the Department of Urology of the Nagoya City University Medical School Hospital.

The material consisted of 94 cases of benign prostatic hyperplasia, 14 cases of carcinoma of the prostate, 5 cases of non-specific prostatitis, and 8 cases of normal condition of the prostate gland.

Serial transrectal prostatography was done in 10 of the 94 cases of benign hyperplasia, in order to estimate reproducibility of the method.

The details of the improved technique are as follows: Antibiotics are administered for 2 days before the day of prostatography. The patient is prepared the evening prior to prostatography with a cleansing soap suds enema. This is repeated the morning of the examination. Half an hour prior to the examination, 0.5 mg. of atropin sulfate and 50 mg. of hydroxyzine is given. In order to obtain adequate relaxation of the anal sphincter, low spinal or saddle block anesthesia was chosen. We have recently used caudal block anesthesia with good results. Preliminary plain roentgenograms of the urethral region, pneumocystograms and injection cystourethrograms are taken on all subjects. All punctures of the prostate gland are done with the patient in the standard lithotomy position. Injection of negative contrast material (air) is made through the urethral catheter. The anus and surrounding areas are prepared with mild antiseptic, and sterile drape and towels applied. A digital examination of the prostate is then done and the sites appropriate for puncture are selected. A 17 gauge

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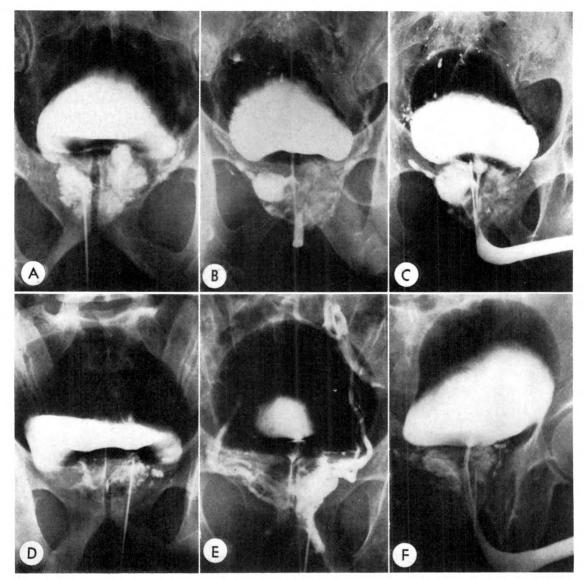


Fig. 1. Transrectal prostatograms showing conditions of prostate. (A) Anteroposterior view of normal prostate. (B) Anteroposterior view of inflammation of prostate. (C) Left anterior oblique view of B. (D) Anteroposterior view of inflammation of prostate. (E) Anteroposterior view of benign hyperplasia in early stage type. (F) Left anterior oblique view of benign hyperplasia in early stage type. In these prostatograms, the surgical capsule of the prostate is not visualized clearly.

needle of 12 to 15 cm. length is used to obtain good results. The bevel of the needle is placed against the pad of the lubricated left index finger. Under television fluoroscopy, the needle is then inserted through the rectal wall into the center of one lobe of the prostate gland. The needle is joined to the injecting syringe containing 20 ml. of contrast medium and 250 mg. of pyrrocyclin (PRM-TC) on the palm of the left hand, then the injection is made manually.

Serial prostatograms are taken during and immediately after the injection. The patient is then placed in the left anterior oblique position and an injection cystourethrogram is taken during the second injection of contrast material into the prostate. The films are exposed using a rapid cassette film changer. Additional information can be obtained by television monitor, or records can be made by utilizing cineradiography. Twenty to 40 ml. of 76 per cent methyl-

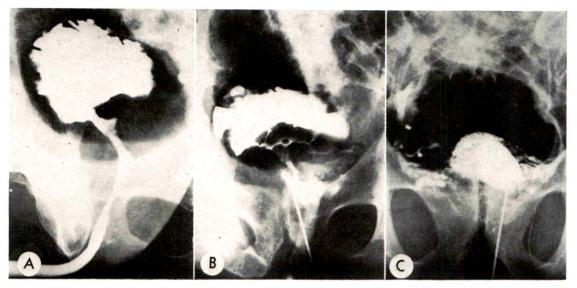


Fig. 2. Findings in carcinoma of prostate. (A) Injection cystourethrogram. (B) Anteroposterior view of prostatogram of A reveals filling defect caused by the carcinoma. (C) Filling defect in the apical region. Contrast material has hardly penetrated into the carcinoma area.

glucamine diatrizoate (renografin 76) is used as the contrast material. Antibiotics and an antiplasmin drug (trans-aminomethyl-cyclohexane carboxylic acid) are given twice a day for 1 or 2 days for the prevention of infection and as a hemostatic. An indwelling catheter is commonly left in place for at least 24 hours following the procedure.

#### RESULTS

A total of 138 transrectal prostatographies using television fluoroscopy were performed on 121 patients. In order to estimate the reproducibility, serial examinations were done in 10 of 94 cases of benign hyperplasia: the same findings were obtained in every patient.

Normal and pathologic conditions of the prostate, including benign hyperplasia, carcinoma and inflammatory disease, resulted in various contrast changes.

The characteristic prostatograms in normal condition, inflammatory disease and benign hyperplasia in an early stage showed units of branched, follicle-like tubules which make up the outer, or true, prostatic glands. In these prostatograms, the prostatic capsule was not clearly visualized (Fig. 1, A-F).

The prostatogram of the diffusely hard prostate, recognized clinically as "typical" carcinoma, showed a filling defect corresponding to the location of the carcinoma, and injection of contrast material into the carcinoma was usually difficult; *i.e.*, very increased pressure was needed (Fig. 2, A-C).

A clear contour was obtained in the roentgenograms of all cases of benign hyperplasia, especially in the late stage type. Filling with contrast material of both lobes gave a more satisfactory picture, although the contour of the prostatic gland could be obtained by a single injection into the one lobe (Fig. 3, A-F). In 12 cases of benign hyperplasia, the hyperplastic mass in both lobes and the surgical capsule could be clearly visualized (Fig. 4, A-C). The elevated floor of the bladder, which had not been well demonstrated on the pneumocystogram, became quite evident in some cases.

It was found that the periprostatic plexus or the small vessels of the surgical capsule were visualized immediately following injection of 3 to 4 ml. of contrast material into the benign hyperplastic mass. This phase is designated by us as the "vascular or plexus phase" (Fig. 5, A-C; and 6,

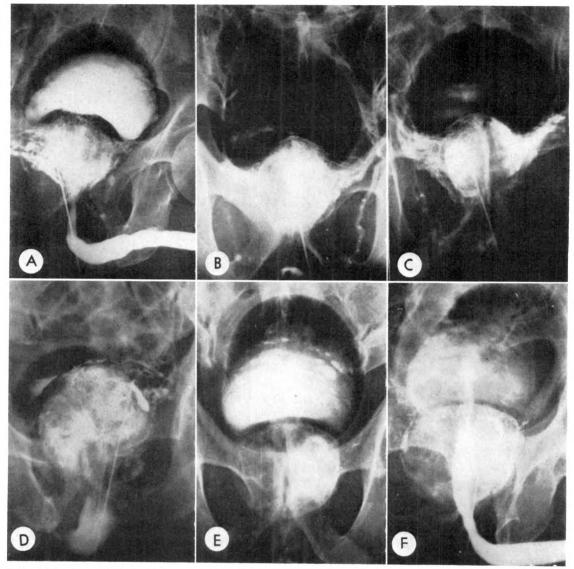


Fig. 3. Contour of prostatic hyperplasia in late stage type by a single injection into one lobe. (A) Left anterior oblique view of right lobe puncture: prostatic phase. (B) Anteroposterior view of left lobe puncture: prostatic phase. (C) Anteroposterior view of right lobe puncture: prostatic phase. (D) Anteroposterior view of left lobe puncture: prostatic phase. In the prostatic phase the surgical capsule, the hyperplastic gland and the phlebogram of the surrounding structures of the prostate are visualized. (E) Anteroposterior view of left lobe puncture: glandular phase. (F) Left anterior oblique view of E. Left lobe puncture: glandular phase. In the glandular phase the opaque medium is still retained in the hyperplastic adenoma.

A and B). Additional injection of contrast material revealed the surgical capsule, hyperplastic gland and sometimes the phlebogram of the surrounding vessels of the prostate. This phase is designated as the "prostatic phase" (Fig. 3, A-D; and 4, A-C). We call the roentgenologically "glandular or adenoma phase" the condition in which opaque medium remains only in the

hyperplastic prostate, after the disappearance of the phlebogram of the surrounding vessels of the prostate and the periprostatic plexus contour (Fig. 3, E and F). Any periprostatic plexus deposits of contrast material are quickly and completely absorbed into the vena hypogastrica through the venae pudendae internae and the venae vesicales inferiores, but extravasation of

# IRRADIATION OF THE LIVER IN CHILDREN: ACUTE EFFECTS ENHANCED BY CONCOMITANT CHEMOTHERAPEUTIC ADMINISTRATION?\*

By MELVIN TEFFT, M.D.,† ANNA MITUS, M.D.,‡ and NORMAN JAFFE, M.B., B.Ch.‡

PREVIOUSLY, we have described our experience with irradiation of the liver in children. 1,12,13 We have noted a low incidence of clinical manifestations of liver failure, referred to as "radiation hepatitis," as reported by others. 5,6 We have postulated that this difference in incidence is related to:

- (a) the volume of liver which is irradiated. In the majority of our patients, the entire liver volume was not irradiated. Therefore, an unirradiated segment was available for hypertrophy and regeneration to preserve normal liver function. This would be in contrast to other reports where the total volume of liver was usually irradiated.
- (b) the integrity of normal liver function at the time of hepatic irradiation. In most of our patients, a portion of normal liver was included in the portal for irradiation of the tumor bed following removal for Wilms' tumor or neuroblastoma. Compromise of normal liver by metastases was not present. Again, this is in contrast to reports by others where the entire liver volume is compromised by widespread metastatic dissemination.
- (c) total dose of irradiation delivered. In most cases, total doses to a portion of irradiated normal liver did not exceed 3,500 rad, delivered in 3½ weeks.\* In other reports, this dose was often exceeded and was referred to as a "threshold dose"; however, lower doses have also been reported as causing adverse liver effect.<sup>6</sup>

Therefore, differences between our experience and that of others possibly is due to the fact that only a portion of normal liver has been irradiated and to doses which do not exceed 3,500 rad in  $3\frac{1}{2}$  weeks.

The gross findings at laparotomy, following irradiation, have been correlated with the histologic changes, which are relatively specific; 1,9 we have described the evolution of these changes as a function of time following irradiation. 12 The radioisotope liver scan has been used to evaluate and monitor these changes, and this has been correlated with routine laboratory tests of liver function, 12 with findings similar to those described by others. 5 More recently, we have described the angiographic appearance of the liver during the acute and later phases of irradiation effect. 7

We have noted an unusually severe peripheral thrombocytopenia (relative to the peripheral leukopenia) which has developed during the "acute" phase of irradiation of the liver. This has been correlated with volume of liver irradiated and dose delivered, and has not been observed during the late or "chronic" phase of radiation effect. A relationship between this unusually severe thrombocytopenia and liver irradiation has been related further to the possible effect of concomitant administration of antitumor chemotherapy. 12

This report is to describe 3 patients, seen recently, whose clinical course seems to emphasize a relationship between irradiation to liver and development of liver abnormality, on the one hand, and either concomitant or later administration of antitumor chemotherapeutic agents on the other hand.

The first case is presented to illustrate

<sup>\*</sup> Five equal fractions per week.

<sup>\*</sup> From the Departments of Radiation Therapy, Children's Hospital Medical Center,† and the Children's Cancer Research Foundation,‡ and from the Departments of Radiology† and Pediatrics‡ at the Harvard Medical School, Boston, Massachusetts.

our previous contention that the administration of certain chemotherapeutic agents may accentuate underlying liver sensitivity caused by irradiation, even when such agents are administered following the completion of irradiation, if such administration is within the acute phase of liver irradiation effect, i.e., approximately 6 months of irradiation. The other 2 cases are presented to illustrate our belief that certain antitumor drugs are toxic to liver "sensitized" by concomitant or prior irradiation, and that the unirradiated portion of liver may be "sensitized" likewise, as it attempts to hypertrophy and assume the major role of liver function, while the irradiated portion becomes fibrotic and shriveled.

#### REPORT OF CASES

Case I. This 13 year old boy was observed to have a large right abdominal mass which extended to the pelvis and beyond the midline into the left hemiabdomen. Arteriography confirmed its intrarenal origin and revealed it to be composed of highly vascular but abnormal (tumor) vessels. Biopsy of an enlarged inguinal lymph node revealed (metastatic) Wilms' tumor.

Because of the size of the mass, he received preoperative treatment with irradiation and chemotherapy; 700 rad\* in 8 elapsed days was delivered to the entire abdomen, including the inguinal lymph nodes. In addition, he received 0.05 mg./kg. body weight vincristine† on 2 occasions, 4 days apart.

The mass regressed markedly and he underwent excision of the tumor and right kidney, in continuity, within 2 weeks of the start of preoperative treatment.

Following surgery, he received additional irradiation to the entire abdomen, with shielding of the left kidney; 2,750 rad was delivered in 45 elapsed days. During this second course of irradiation, following delivery of 1,050 rad in 8 elapsed days, treatment was interrupted due to an abrupt depression of the peripheral blood cell counts, but was reinstituted after 10 days (Fig. 1).

Concomitant with irradiation, he received actinomycin D (70  $\gamma$  per kg. body weight in 7

evenly divided doses) immediately following surgery.

He remained well, with no further treatment, over the next month, when he was then noted to have developed metastases to the left femoral shaft and to lymph nodes in the left supraclavicular fossa;  $3,\infty$ 0 rad in 30 elapsed days was delivered to each of these local areas. In addition, he received actinomycin D (70  $\gamma$  per kg. body weight in 7 evenly divided doses) and vincristine (0.05 mg./kg. body weight), the latter on 2 occasions, I week apart, during the actinomycin D administration, and concomitant with irradiation.

At the start of his therapy, on this occasion, his peripheral blood cell counts were at normal levels. One week following completion of actinomycin D and the second dose of vincristine, he developed a marked peripheral pancytopenia (Fig. 1). At this time, his radioisotope liver scan, which had been normal, including a scan obtained just prior to this new course of chemotherapy, showed a diminished distribution of radiocolloid in liver, and an increased concentration, with reversal of ratio, in favor of the spleen, which became enlarged (Fig. 2,  $\Lambda$  and B).

Three months previously, his liver function tests had been normal (SGOT, 50; alkaline phosphatase, 4.2 Bodansky units; bilirubin, 0.7 direct/1.7 mg. total). They now became abnormal: SGOT, 130; alkaline phosphatase, 17.9 Bodansky units. Bone marrow aspirate at this time was "hypocellular."

After I week had elapsed, during which time he received supportive care, including platelet transfusions, his peripheral blood cell count rose toward normal levels and his isotope scan became normal (Fig. 2C). At no time did he manifest clinical signs or symptoms of liver dysfunction, other than transient splenomegaly.

Since this time, he has been well, without further signs of hepatic dysfunction; he has remained free of active disease for the last 6 months. Further administration of chemotherapy, within the past 3 months, or more than 6 months following irradiation, has consisted of actinomycin D and vincristine as a maintenance program, in doses similar to the above and without obvious peripheral blood cell count depression or liver abnormality.

Comment. The first episode of acute thrombocytopenia, which occurred during his initial therapy to the abdominal primary lesion, may be related to factors observed in other patients and reported previously.<sup>12</sup> Briefly, we have

<sup>\*</sup> Except as noted, the factors were: 250 kvp., 15 ma., 0.4 mm. Sn, 0.25 mm. Cu, 1.0 mm. Al added filter, hvl. 2.8 mm. Cu.

<sup>†</sup> In all cases, chemotherapy was administered under the direction of Doctor Sidney Farber.

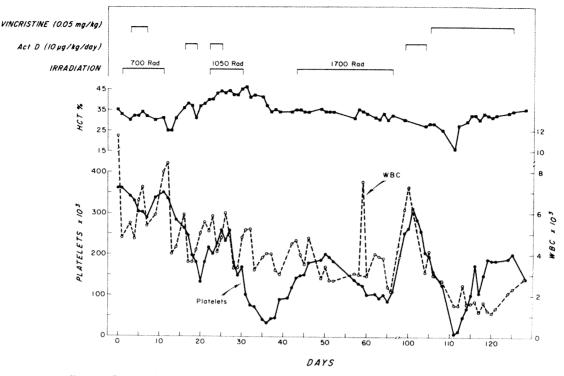


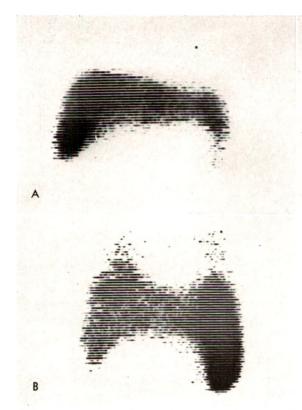
Fig. 1. Case 1. Graph of peripheral blood cell counts relating irradiation to antitumor chemotherapy. Day "o" is defined as the day of diagnosis.

postulated that during irradiation, the irradiated liver segment undergoes the "acute" phase of irradiation effect, which includes various degrees of congestion and regeneration, depending on dose, volume treated and possibly age of the patient. The unirradiated liver segment "reacts" to this by beginning to undergo compensatory hypertrophy to maintain normal liver function. The end result is consistent with previous descriptions of a fibrotic and contracted irradiated segment and an enlarged hypertrophied unirradiated segment.

In the acute stage of irradiation effect, therefore, acute congestion may be reflected in elevation of pressure in the portal bed with possible secondary hypersplenism. Moreover, in its acute stage of irradiation effect, the regenerating liver is mitotically active and adversely affected by various chemotherapeutic agents, such as actinomycin D.4.8.11 This adverse effect by chemotherapy, administered at the time of irradiation, or any time during this acute phase of irradiation effect (therefore administered at any time within 6 months of irradiation) may increase the tendency to liver dysfunction over that due to irradiation alone. Thus, congestion of the liver and portal bed may be increased and obvious secondary hypersplenism may ensue with active trapping of peripheral blood cell elements. Our previous report, which included a platelet survival study in I patient, would tend to verify this.<sup>31</sup>

Furthermore, this increased sensitivity and tendency to liver dysfunction, may reduce the ability of the liver to excrete the chemotherapeutic agent, giving an increased titer of circulating agent and increased toxicity.<sup>10</sup> In the case of actinomycin D, the acute and severe peripheral blood cell count suppression, especially thrombocytopenia, as noted in this case, might be expected.

The recurrence of this phenomenon, but to a more severe degree, approximately I month following completion of irradiation of liver, and during chemotherapy administration, as noted in this patient, is probably due to the continued acute effect of the liver sensitized from prior treatment after it had now received full dose irradiation. Our past experience has noted a significant increase in this phenomenon when larger volumes of liver are irradiated, and to the higher doses. The fact that the entire liver volume was irradiated to relatively high dose in this patient, may indicate a tendency for this to have occurred, since unirradiated tissue was not available for compensation.



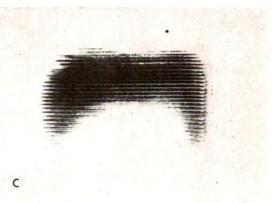


Fig. 2. Case 1. Tc<sup>99m</sup> sulphur colloid liver scan, obtained prior to the second course of chemotherapy, shows a normal distribution of isotope in the liver and a normal ratio of distribution between liver and spleen. The spleen is normal in size. (B) Tc<sup>99m</sup> sulphur colloid liver scan, obtained 1 week following completion of a second course of chemotherapy, when the peripheral blood cell counts showed an acute suppression, reveals inhomogeneous distribution of isotope throughout the liver and an increased amount of radioisotope relative to the liver in an enlarged spleen. (C) Liver scan, 2 weeks following

B, is normal, both in the distribution of radiocolloid in the liver, and in the relative distribution between liver and spleen. The spleen size is normal.

In this case, the liver scanning was a useful method to document and monitor liver function abnormality. The diffuseness of the abnormality is consistent with the fact that the entire liver volume received irradiation.

Case II. This  $2\frac{1}{2}$  year old boy developed a left-sided abdominal mass; intravenous pyelography indicated that it was intrarenal. Preoperative vincristine was administered in doses similar to those described previously and the mass decreased in size. He was referred to Children's Hospital Medical Center where he underwent laparotomy. A large Wilms' tumor was excised in continuity with the left kidney; tumor was found in the renal vein and the inferior vena cava.

Following surgery, he received irradiation to the left renal fossa, which included the left hepatic lobe, and both lung fields. The latter entailed irradiation of the upper 1/3 of the volume of the right lobe of liver; 3,175 rad in 40 days was delivered to the left renal fossa, including 1,200 rad in 9 days to both lung fields, in continuity. In addition, he received actino-

mycin D in doses as described above and one injection of vincristine.

At the completion of the course of actinomycin D, and following delivery of 1,200 rad in 9 days to both lung fields and 1,575 rad in 13 days to the left renal fossa, he developed a depression of peripheral blood cell counts, with a relatively severe thrombocytopenia which caused temporary discontinuation of irradiation and further vincristine therapy (Fig. 3).

Up to this time, his liver scan had been normal. However, now he developed a localized area of diminished radioisotope concentration in the right lobe of liver (Fig. 4, A-C). Hepatic arteriogram revealed obstruction of hepatic venous flow at the site of abnormality by liver scan, with collateral filling of intrahepatic portal veins; adjacent to this area was a region of hypervascularity (Fig. 5, A-D).

Because of the depressed blood cell counts, laparotomy for biopsy was not possible. Over a period of approximately 10 days, as his blood cell counts rose to more normal levels, his liver scan became normal.

During the time of his liver scan abnormality

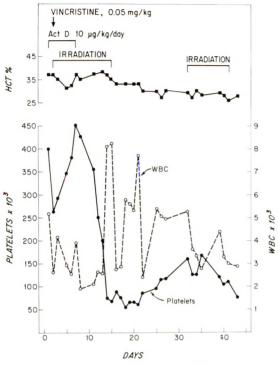


Fig. 3. Case II. Graph of peripheral blood cell counts relating irradiation to antitumor therapy. For description of irradiation, see text.

and depressed peripheral blood cell counts, he failed to show any clinical signs or symptoms of liver failure. Liver function tests remained normal at all times (SGOT, 50; direct bilirubin 0.1 mg./total 0.6 mg.; alkaline phosphatase, 6.5 Bodansky units; total protein, 7.9 gm., albumin, 5.2 gm.).

He completed irradiation to the left renal fossa without incident. At no time since (over the past 6 months) has he shown abnormality by liver scanning; his peripheral blood cell counts have remained satisfactory. Moreover, he has been able to tolerate repeated courses of actinomycin D and vincristine during this time.

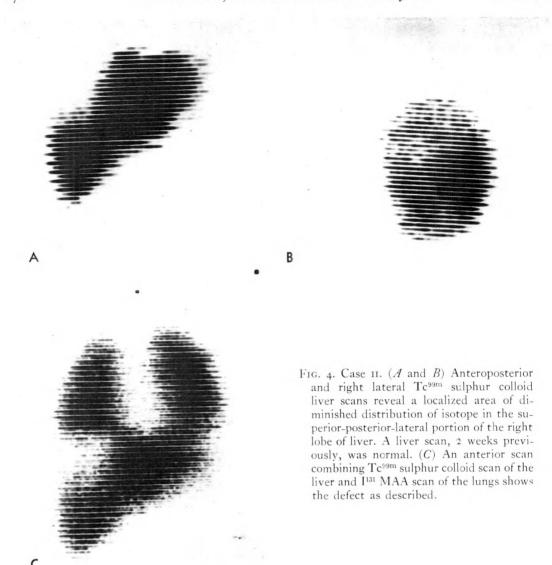
Comment. At the time of the occurrence of the abnormality by liver scan and arteriogram, and when peripheral thrombocytopenia had occurred, this patient had received relatively low dose irradiation to segments of liver, plus chemotherapy. Specifically, the area of abnormality by scan received 1,200 rad, as it had been included in the inferior portion of the portal for lung irradiation. We may postulate that this was sufficient to cause acute hepatic vein congestion since actinomycin D may have added to the effects of irradiation. Alternatively, we may postulate that actinomycin D adversely

affected the right lobe of liver as it reacted to liver irradiation and this was manifest in the upper portion of the right hepatic lobe. Presumably, the adjacent area of increased vascularity was due to acute congestion. The acute peripheral depression may be due to factors described above, i.e., acute effect on the liver and diminished excretion of the drug secondary to this. The absence of increased splenic uptake may indicate that the degree of effect was not as pronounced as in Case I or our previously reported cases, where the irradiation dose had been higher. We do not believe that this transient phenomenon by liver scan was due to tumor metastases since, in our experience, Wilms' tumor does not readily regress when it is metastatic to liver and without more aggressive therapy.

Case III. This 7 year old girl had a Wilms' tumor excised from the left renal fossa. Postoperatively, she received 2,340 rad (Co<sup>60</sup>) to the left renal fossa in 16 days, and actinomycin D. Within I month, lung metastases developed and she received a second course of actinomycin D. Over the next 2 months, the lesions regressed; at this time, a third course of actinomycin D was instituted. One month later, the right lobe of her liver became palpable. No liver scan or liver function tests were studied. A clinical diagnosis of liver metastases was made, and she was treated with vincristine sulfate. Over the ensuing few weeks, her liver diminished to normal.

She was referred to Children's Hospital Medical Center where examination revealed a nonpalpable normal liver. Liver scan was normal (Fig. 6A). Chest roentgenogram and peripheral blood cell counts were also normal.

She was treated with another course of actinomycin D and vincristine was continued. During this time, she developed sudden thrombocytopenia (her platelets fell from 240,000 to 90,000 within 2 days). Her white blood cell count was no lower than 4,300 and her hematocrit was 32 at this time. Her liver became palpable 6 cm. below the right costal margin. One week later, a repeat liver scan revealed diminished uptake in the unirradiated right hepatic lobe and increased uptake in the spleen (Fig. 6B). Hepatic arteriogram revealed stretching of the intrahepatic vessels in the right lobe but no tumor vasculature. Interpretation was acute congestion in the liver with stretching of vessels with no evidence of metastatic disease. Two weeks later, when her peripheral blood cell



counts were normal, her liver scan was repeated and was also normal (Fig. 6C).

Since then, a repeat course of actinomycin D has not resulted in liver scan or peripheral blood cell count abnormality. At no time did she show clinical liver dysfunction, and liver function tests remained normal at all times.

Comment. We postulated that following irradiation to the left lobe of the liver, the right lobe underwent hypertrophy and regeneration. During this acute stage, actinomycin D was administered. The sudden increase in size of the liver, which was believed to be due to metastases, may have been due to acute congestion of irradiation and enhanced by actinomycin D. Later on, the scan defect, which

occurred during further actinomycin D: ministration, and still within 6 months of radiation to the liver, may have been due actinomycin D toxicity on the unirradiated l hypertrophying and "regenerating" right lo of liver which was mitotically active and ser tized to actinomycin D. The increased upta in the spleen may have reflected the acr effect with secondary increased hyperspleni as described previously. We believe that can rule out the possibility of intrahepa metastases by the transient nature of this p nomenon and the return to normal of the liscan. In our experience, liver metastases do 1 regress with such alacrity to any form of ar tumor therapy.

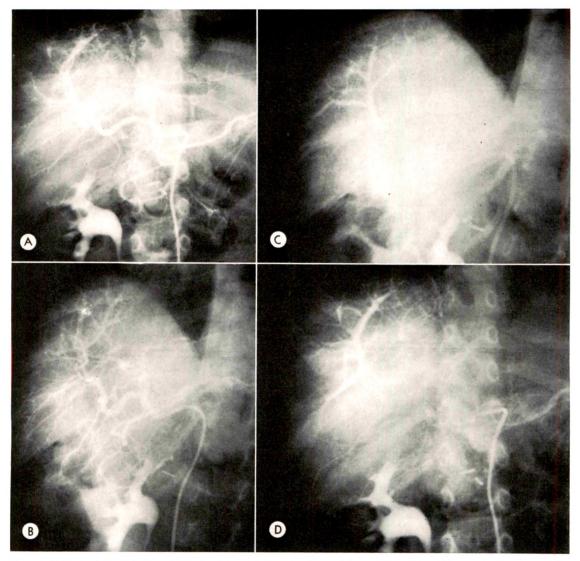


Fig. 5. Case II. (A-D) Celiac angiograms reveal the vessels in the medial aspect of the upper portion of the right hepatic lobe to be slightly stretched (A) about an area of increased vascularity (B). There is evidence of obstruction to hepatic venous outflow with shunting of blood into hepatic portal veins just lateral (C and D).

Her ability to tolerate later courses of actinomycin D indicates the reversal of this effect and the fact that such was administered after the acute stage of congestion and regeneration had passed, when the liver had passed into the chronic phase of irradiation effect and was therefore less sensitive to actinomycin D administration.

#### DISCUSSION

As we have reported previously,<sup>1,12,13</sup>, irradiation of the liver causes changes histologically which can be divided be-

tween an acute phase, blending into a subacute stage, and thence passing into a chronic phase which is discernible several years later. This is dose related and may be age related; *i.e.*, the more severe changes occur at the higher doses and possibly in the very young child, even at more moderate doses. The production of clinical and laboratory signs of liver dysfunction is dependent upon the volume of irradiation, in addition to the other factors, and is dependent also upon the amount and in-

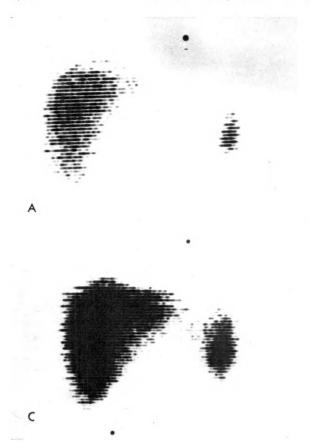




Fig. 6. Case III. (A) Tc<sup>99m</sup> sulphur colloid liver scan shows a normal distribution in the liver and a normal ratio of distribution between the liver and the spleen. The spleen is not enlarged. (B) Repeat liver scan, obtained I week later, shows acute diminution of distribution of isotope in the lateral aspect of the right hepatic lobe with increased distribution in the spleen relative to the liver. (C) Two weeks later, a repeat scan is normal both in the distribution of the radioisotope throughout the liver and the ratio of distribution between the liver and spleen.

tegrity of the unirradiated liver tissue which undergoes compensatory hypertrophy to maintain liver function, as the irradiated segment attempts to undergo regeneration.

The sensitivity of the liver to both irradiation and certain chemotherapeutic agents, in certain abnormal states, such as following partial hepatic resection, has been described.<sup>2,3,8,11,14</sup> Moreover, we have discussed the possible role of the irradiated liver, during concomitant chemotherapeutic administration, in tending to increase "toxicity," both due to the effect on the liver itself by these agents with production of an accentuated portal bed congestion and hypersplenism, and due to an increased titer of the agents with increased bone marrow effect.<sup>13</sup> Our experience with all patients who have received actinomycin D, has shown that an acute and severe thrombocytopenia, relative to leukopenia, is significantly more common in those patients who have received irradiation to relatively large volumes of liver (such chemotherapy having been administered within 6 months of irradiation) at doses between 2,400 and 4,000 rad (average of 3,500 rad). Thus, we have postulated a secondary hypersplenism as at least one of the contributing factors.

As we have noted, the lack of a group of patients who have not received chemotherapy makes this discussion somewhat speculative. However, the significantly increased incidence of thrombocytopenia in patients with significant volume of liver irradiation, as compared to those patients who have had smaller volume of liver irradiated, both groups receiving similar chemotherapeutic agents, tends to give confirmation to our postulate.

The differences noted among these and other patients relative to the observance of acute pancytopenia and scan defects, both during and for a period of 6 months following irradiation, when related to courses of chemotherapy, are believed due to

differences in volumes of liver that are irradiated and in radiation dose that is delivered. Moreover, the role of idiosyncrasy both to liver irradiation and to chemotherapy cannot be neglected.

We advise therefore that these agents be used with caution during this acute phase of liver irradiation (during the first 6 months following therapy) and that frequent liver scans and evaluation of peripheral blood cell counts be obtained during such drug therapy.

As we have noted previously, other forms of liver abnormality, in addition to irradiation effect, such as infection, partial resection, etc., may leave the liver similarly sensitized. Therefore, caution should be used at all times during administration of certain therapeutic agents if any form of liver abnormality exists. This includes the use of irradiation.

#### SUMMARY

Three cases are reported to describe further our experience with antitumor chemotherapeutic agents, administered either during or following irradiation to the liver in children. The scan defect that has occurred acutely and the peripheral blood cell count depression make us believe that these agents are toxic to liver which is irradiated in whole or in part; further, that the unirradiated segment may be adversely affected by these agents since it is in a sensitive state of compensatory hypertrophy; and that such defects can occur suddenly after the completion of irradiation when certain chemotherapeutic agents are administered within 6 months of the completion of irradiation.

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### METHODS FOR THE ENHANCEMENT OF SKIN SPARING IN COBALT 60 TELETHERAPY\*

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UNDER most conditions encountered in radiotherapy, cobalt 60 beams are skin sparing, the dose in the skin being a fraction of the maximum dose which occurs in the subcutaneous tissues. In many situations, however, skin sparing is lost, and it has been estimated16 that about 2 per cent of cases treated with supervoltage radiation for deep-seated malignancies experience significant skin reactions. Furthermore, skin tolerance is often the limiting criterion in the palliation of metastatic disease, especially when the technique involves a single treatment.22 Other current trends in cobalt 60 teletherapy which increase the skin dose are the use of penumbra trimmers, and the increasing use of the isocentric method of treatment, both of which often bring the collimator or other scattering material close to the skin. In an effort to reduce penumbra, scatterers have recently been placed as close as 8 cm. from the skin in treatments with large

One phenomenon of interest is the response of skin to cobalt 60 beams as a function of the area of the treatment field. For orthovoltage radiations this response has been well studied and reduced to arithmetic form;23 however, for cobalt 60 beams the study of the physiologic response of the skin, which may exhibit areal dependence, first requires a method for the estimation of the actual dose in the skin, which certainly exhibits a strong areal dependence. It has long been known that the dose in the very superficial layer is the most important factor affecting the skin reaction in cobalt 60 teletherapy.3

> SKIN SPARING AND ELECTRON CON-TAMINATION OF GAMMA-RAY BEAMS

Every gamma-ray beam used in radio-

therapy is contaminated with secondary electrons. These electrons arise from photon interactions in the air, in the collimator, in the beam shaping blocks, and in the supporting fixture for the shaping blocks, commonly called the "shadow tray." The effect of these electrons is to increase dose in the skin relative to the dose in the subcutaneous tissues. If for every 2 electrons absorbed in the subcutaneous tissue, only I electron is absorbed near the skin surface, there is satisfactory skin sparing; however, if the same number of electrons are absorbed at both depths there is no skin sparing at all. If all of the electrons could be removed from the beam the dose on the skin surface would be zero, neglecting backscatter, regardless of the dose at depth. On the other hand, if the radius of the treatment field were made as large as the electron range in air, the surface dose would be equal to the subcutaneous dose under all conditions. A recent detailed discussion of this concept has been given by Dutreix et al.6 Clinical situations lie between these two theoretical extremes; the surface dose is never zero, and it is usually less than the peak dose which occurs at the equilibrium depth.

The measurable quantity of interest is the ratio of the absorbed dose near the skin surface to the peak dose. This ratio has been variously designated the "surface ionization ratio,"8 the "build-up ratio,"21 the inverse of the "build-up ratio,"15 the inverse of the "build-up factor," and the "relative surface ionization." In this paper we will use "relative skin dose," realizing that it is the quantity of interest rather than the precise quantity measured.

The data reported were measured in the usual manner with an ionization chamber and electrometer. The "window" of the

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chamber consisted of aluminized mylar having a thickness of 10 microns. The chamber could be fitted with a lucite cap, and the ratio of the reading without the cap to that with the cap is the reported quantity, a small correction being applied for attenuation in the cap.

## SKIN SPARING AND THE ATOMIC NUMBER OF THE SCATTERER

Whenever electrons are incident on a scattering material, or are generated within the material by the absorption of a photon beam, they are scattered many times and at all forward and backward angles by the electrons and nuclei of the scatterer. According to modern scattering theory, the number of scattering events per unit thickness of scattering material, and consequently the fraction of the electrons which are scattered at any particular angle, is directly proportional to the square of the atomic number of the scatterer, and inversely proportional to the square of the electron energy. This effect was first observed in radium therapy,17 and Wilson and Perry<sup>24</sup> studied the effect for 1 and 2 mev. x rays. Hine apparently performed the first systematic study of the effect for various atomic numbers and photon energies.

Figure 1 shows how the relative skin dose varies with Z, the atomic number of the scattering filter. Obviously for cobalt 60 beams the relative skin dose is least for

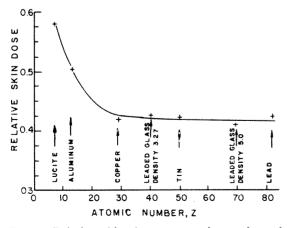


Fig. 1. Relative skin dose vs. atomic number of electron filter. Cobalt 60; 15×15 cm. field.

intermediate and high Z scatterers, confirming the results of others.<sup>5,19</sup> The important point is that commercial leaded glass, in densities of 3.2 or greater, is as effective as the pure metals in reducing the skin dose.

The use of metallic electron filters for routine cobalt 60 therapy has been suggested;<sup>5,18</sup> however, such filters have not come into common usage, probably because of their opacity to light. Lucite and leaded glass offer the advantage of transparency, and the effect of lucite shadow trays on skin sparing has recently been reported;<sup>13</sup> however, the large difference in the skin dose for these 2 materials dictates in favor of leaded glass when skin sparing is important.

As with any build-up material the filter thickness needs to be just sufficient to stop all electrons arising on the source side of the filter. This would require less than 1 mm. of density 3.27 glass; however, a practical thickness, from the standpoint of strength and economy, is about 1/8 inch. A filter of this thickness will attenuate the beam by about 7 per cent, and will cause negligible refraction of the light field when mounted normal to the primary beam.

Scattering theory predicts that not only will more electrons be scattered out of the beam for intermediate and high Z materials, but that more will be backscattered within the filter, resulting in fewer electrons emerging from the surface. This has been confirmed clinically for Co<sup>60</sup> by Simon *et al.*<sup>20</sup> who demonstrated that treatments through a brass filter placed on the skin gave much less severe reactions than treatments through either a plexiglass filter or with the open beam.

A leaded glass electron filter which is used routinely on a busy therapy unit will receive on the order of I megarad per year, and must therefore be a well stabilized non-browning glass. Any high grade commercial shielding glass should meet this requirement; however, the authors have tested only Corning No. 8362 shielding glass. For this glass a cobalt 60 exposure

of 11 megarad yielded a change of less than 0.02 in optical density.

# THE DEPENDENCE OF SKIN SPARING ON FIELD SIZE AND SCATTERERSKIN DISTANCE

The dependence of the relative skin dose on the scatterer-skin distance has been reported by several authors for cobalt 60 teletherapy units of various design.<sup>2,7,8,15,19,21</sup> Our measurements were made on the AECL Theratron 80 unit.

The strong dependence of the relative skin dose on both the scatterer-skin distance and the field size is shown in Figure 2 for a lucite filter. In the Figure h is the distance between the skin (ionization chamber) and the electron scatterer, whether it be the collimators, the leaded glass filter, or the metallic filters. The radius of the circular field, having an area which is equivalent for backscatter and depth dose purposes to the indicated field size, is indicated by r. In order to limit the relative skin dose to 0.5 for the  $5 \times 5$ ,  $15 \times 15$ , and  $30 \times 30$  cm. fields, the skin must be at a distance of 3.4 cm., 13 cm., and 33 cm., respectively. Clearly there is very little skin sparing for the larger field sizes at the scatterer-skin distances normally employed with isocentrically mounted units.

Figure 2 also demonstrates the significant improvement in skin sparing which can be achieved with a leaded glass filter. With this glass filter the relative skin dose can be limited to 0.5 for scatterer-skin distances of about 20 cm. or less, regardless of the field size.

One other conclusion can be drawn from inspection of Figure 2. From the asymtopic nature of the curves it appears that, regardless of the filter or field size used, optimum skin sparing occurs for an h/r value of about 4. This is easily achieved for the  $5\times 5$  cm. field, since it only requires a distance of 12 cm.; however, it is hardly possible with an isocentric unit for the 30  $\times$ 30 cm. field, since the corresponding scatterer-skin distance is 67 cm.

It should be pointed out that the equivalent field size principle applies for skin sparing as it does for depth dose and back-scatter calculations. As an example, whenever a 35×35 cm. "mantle" field is applied to a patient, the lung blocks define an equivalent field of only about 14×14 cm. over the mediastinum; thus allowing a large reduction in the scatterer distance for the same degree of skin sparing. This has been measured using LiF by Anderson, D'Angio and Khan, and confirmed in our department by ionization measurements.

Figure 3 shows the relative skin dose for various filters and the open beam (no filter), for different field sizes and distances. Comparing lucite and the open beam it is seen that lucite, which is an efficient source of

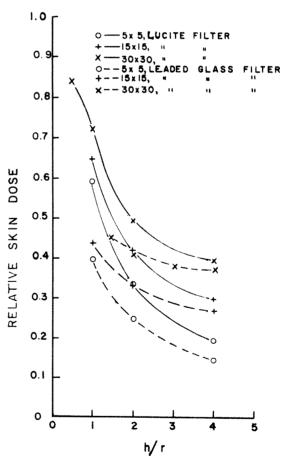


Fig. 2. Relative skin dose vs. the ratio h/r for cobalt 60. Comparison of lucite and leaded glass (density 3.27) electron filters for 3 field sizes.

secondary electrons, gives more skin sparing for the smaller field sizes by intercepting the electrons scattered from the collimators. The cross-over point for this effect occurs for a field size of about 10×10 cm. for the Theratron 80 unit.

A final, and perhaps the most important conclusion which we may draw from these figures is that a leaded glass filter, of intermediate effective atomic number, results in greater skin sparing than a lucite filter, or the open beam, for all field sizes and for all scatterer-skin distances used routinely.

## SKIN SPARING AT TANGENTIAL INCIDENCE

Whenever a cobalt 60 beam is incident tangentially upon the skin, the maximum dose occurs quite close to the surface, and skin sparing is lost to a large degree. This effect has been reported for cobalt 60 and cesium 137 beams<sup>3</sup> and for 2 mv. x rays.<sup>12</sup>

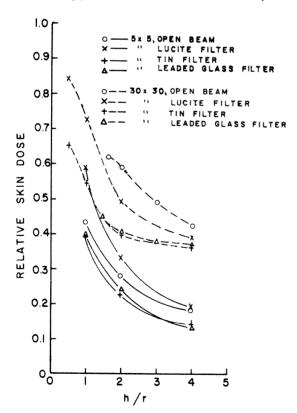


Fig. 3. Relative skin dose vs. the ratio h/r for cobalt 60. Comparison of various electron filters with the open beam for 2 field sizes.

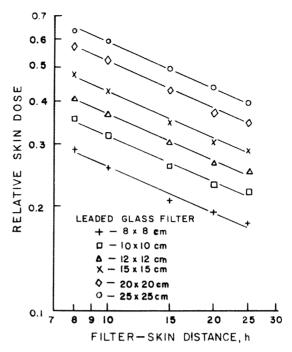


Fig. 4. Relative skin dose vs. filter-skin distance for a leaded glass electron filter (density 3.27). The slope of the lines is -0.44.

Since the effect is due largely to phenomena other than electron contamination of the beam, the addition of a filter of any kind will have a negligible effect on the relative skin dose.

## ANALYTIC EXPRESSION FOR THE RELATIVE SKIN DOSE

In external beam treatment planning, whether by manual or computerized methods, it is useful to have an analytic expression for the constraints. The relative skin dose under a leaded glass filter was measured for field sizes of  $8\times8$  to  $25\times25$  cm., and for filter-skin distances of from 8 cm. to 25 cm., these being the values normally encountered in treatment situations. The results, which are plotted in Figures 4 and 5, indicate that the relative skin dose is a simple power function of both h and r. A least squares fit of these data yields the expression,

Relative Skin Dose =  $0.25h^{-0.44}r^{0.72}$ .

It is apparent from this expression that the

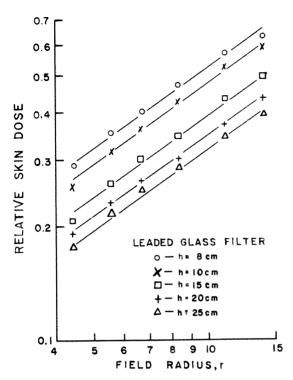


Fig. 5. Relative skin dose vs. field radius for a leaded glass electron filter (density 3.27). The slope of the lines is 0.72.

field size is a more important parameter than the filter-skin distance, a point which has not been stressed previously in the literature. The agreement between the analytic expression and the experimental data is given in Figure 6.

#### SUMMARY AND CONCLUSIONS

- sparing effect can be enhanced, for all field sizes and filter-skin distances, by use of a leaded glass electron filter having a density of at least 3.2 gm./cm.<sup>3</sup>. This will result in a 20–30 per cent decrease in relative skin dose over a lucite filter or the open beam. Leaded glass filters are as effective as pure metals in reducing the skin dose. The filter thickness needs to be just sufficient to stop all electrons arising on the source side of the filter.
- 2. The relative skin dose depends upon the field size and, to a lesser degree, upon the filter-skin or collimator-skin distance.

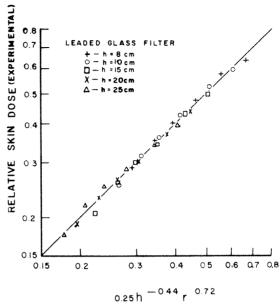


FIG. 6. Comparison of analytic expression for the relative skin dose with experimental results. The 6 points for each value of h represent field sizes of 8×8 cm., 10×10 cm., 12×12 cm., 15×15 cm., 20×20 cm., and 25×25 cm. Data apply to cobalt 60 irradiation through density 3.27 leaded glass.

Whenever a leaded glass filter is used the relative skin dose can be predicted from the expression,

$$RSD = 0.25 h^{-0.44} r^{0.72},$$

where h is the filter-skin or collimator-skin distance and r is the effective radius of the field on the skin.

3. The common belief that optimum skin sparing is achieved whenever the filterskin distance is at least 20 cm. does not hold for the larger field sizes. Whenever skin sparing is important the value of h/r should be as large as possible, and should be at least 2 when a leaded glass filter is used. For field sizes of  $5\times5$  cm.,  $15\times15$  cm., and  $30\times30$  cm. this requires filterskin distances of 6 cm., 17 cm., and 33 cm., respectively.

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# USE OF ELECTRON FILTER TO REDUCE SKIN DOSE IN COBALT TELETHERAPY\*

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ONE of the clinical advantages of high energy x-ray or gamma-ray beams is the skin sparing effect. However, this effect may be lost if the diaphragm of the therapy unit is close to the skin surface. Similar problems arise if an absorber of low atomic number is placed near the skin.

It has been shown<sup>3</sup> that an air gap of 15 to 20 cm. between the diaphragm (or absorber) and the skin is adequate to absorb or scatter most of the secondary electrons present in the gamma-ray beam before entry into the tissue. The electron contamination may also be reduced by gammaray absorbers of medium atomic number which give minimum electron scatter in the forward direction.<sup>1,2,4–6</sup>

This communication discusses the effect on the skin dose when such an absorber (tin) is used at various distances from the skin surface.

#### EXPERIMENTAL ARRANGEMENT

The experimental arrangement is shown in Figure 1. A Co<sup>60</sup> beam is incident on a presdwood phantom of density 0.99 g./cc. A uniform layer (thickness=0.38 ±0.02 mm.) of LiF powder was placed in level with the phantom surface and a similar layer of LiF was placed at 0.5 cm. depth in the phantom. Both layers were located at the center of a 20×20 cm. field generated at a SSD of 80 cm. The cobalt 60 unit was an Eldorado-8 with a source-to-diaphragm distance of 45 cm.

Without any absorber in the beam the "surface dose"\* was measured as a percentage of the dose at 0.5 cm. depth in the phantom. Following this, a presdwood sheet, of thickness 1 cm., was interposed in

the beam at various distances from the phantom surface, and the per cent "surface dose" was measured in each case. The experiment was repeated by mounting a tin sheet (0.8 mm. thick) on the undersurface of the presdwood sheet.

Results of the above experiment are presented in Figure 2. As expected, tin gave appreciably less "surface dose" than in the case of the presdwood absorber. The curves give a combined effect of the atomic number and the mounting distance of the absorber on the "surface dose."

#### DISCUSSION

The electron contamination of the beam with no absorber placed in the beam is mainly due to the secondary electron emis-

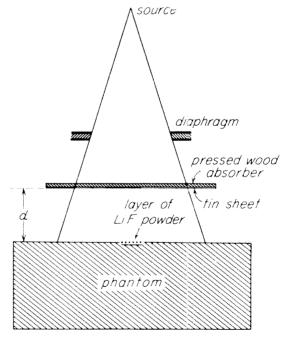


Fig. 1. Experimental arrangement to measure "surface dose" using LiF powder layer.

<sup>\*</sup> The "surface dose" here does not mean the dose at zero depth but the dose at some depth between 0 and 0.4 mm.

<sup>\*</sup> From the Department of Radiology, Division of Radiotherapy, University of Minnesota Hospitals, Minneapolis, Minnesota. Partial support by NIH Grants CA 08-832, CA 08-101 and CA 05-190.

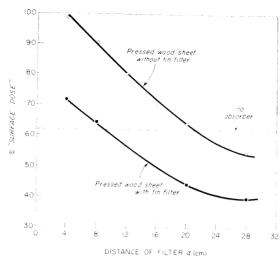


Fig. 2. Variation of per cent "surface dose" with the absorber mounting distance (d). Field size, 20×20 cm.; SSD, 80 cm.; and source-to-diaphragm distance, 45 cm.

sion from the collimator and the source shield. When a low atomic number absorber such as presdwood of thickness greater than the maximum range of the secondary electrons (equilibrium thickness) is introduced in the beam, the collimator and the source shield electrons are almost completely absorbed. However, the secondary electron emission from the absorber itself becomes the source of electron contamination. A tin sheet of equilibrium thickness mounted underneath the presdwood absorber will likewise absorb the electrons from it, and in turn produce secondary electrons because of gamma ray interaction with tin. The electrons generated in tin suffer multiple collisions within the tin absorber, resulting in a relatively less forward scatter than expected in the case of lower atomic number absorbers.

#### CONCLUSION

The use of medium atomic number absorbers (electron filters) such as tin finds a

routine application in radiation therapy set-ups in which a compensator or a lucite tray to support shielding blocks is interposed in the beam. An important practical deduction may be made from this experiment; namely, the introduction of a thin sheet of tin attached to the underside of a low atomic number absorber at a distance of about 8 cm. from the skin brings the skin dose close to the value obtained with no absorber in the beam. While a 0.8 mm. thick sheet of tin attenuates the useful beam by less than 3 per cent, it remarkably reduces the skin dose. It may be mentioned that using a thickness of electron filter greater than the equilibrium thickness does not further improve the skin dose but only causes undesirable attenuation of the gamma-ray beam.

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### A CONTOUR PLOTTING DEVICE\*

By J. LEGAL, A. F. HOLLOWAY, and K. BREITMAN WINNIPEG, MANITOBA, CANADA

WHEN planning external beam radiotherapy treatments, it is often necessary to know the patient's contour along the midtreatment plane, or planes parallel to it.

Several methods for obtaining such contours have been used, varying from the "iron-maiden" type of device with radial spokes of adjustable length to the traditional use of a length of thin soldering compound. Clarke has recently published another design for such a contour device.

A more elegant and accurate device is the Lobravico contour plotter referred to by Moss.<sup>2</sup> In this device the contour plane is established by the instrument and the patient's contour transferred to a paper on the instrument by means of a sliding rod and pen. The rod is free to move in a perpendicular and transverse manner anywhere within the contour plane. The end of the rod is brought into contact with various positions on the patient's skin, at which times a pen on the other end of rod is pressed against the recording paper.

The device as described has limitations as follows: first, it can only accept patients who are in a horizontal position; secondly, the contour may be taken only above the widest portion of the section; and finally, it would be difficult to take several parallel contours, as is desirable in patients who are having treatments about the neck and shoulders.

#### DESIGN

We have constructed a contour plotter (Fig. 1) whose design, while similar to the Lobravico contour plotter, has been modified in such a way as to circumvent these difficulties.

Two motions X and Y are ball bearing supported, allowing the stylus to be brought

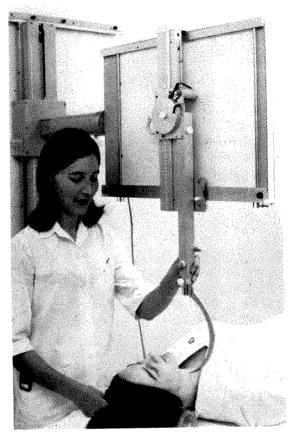


Fig. 1. View of the contour plotting device used for a vertical section.

accurately into contact with the patient's skin. A manually controlled switch just above the stylus operates a solenoid printer at the top of a common beam. The stylus is curved and can be rotated enabling it to reach beyond the widest portions of a patient. Contours can be taken at any angle through the patient, whether he is in a sitting or prone position, by rotating the pantograph. Mounting tracks on the wall make it possible to take a number of contours without disturbing the patient,

<sup>\*</sup> From the Physics Department, the Manitoba Cancer Treatment and Research Foundation, Winnipeg, Manitoba, Canada.

and they also serve to make positioning convenient.

#### CONCLUSION

This device has been used for 2 years, primarily for taking contours, but is also used to transpose field center and direction markings from treatment plans to plastic restraining shells. By removing the stylus and substituting a felt marker, lines indicating the contour plane and the field size may be applied directly onto the patient.

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# THE APPLICATION OF B-SCAN ULTRASOUND IN THE PLANNING OF RADIATION THERAPY TREATMENT PORTS\*

By WILLIAM N. COHEN, M.D., and A. CURTIS HASS, M.D. IOWA CITY, IOWA

CROSS sectional representations of soft tissue structures within the abdomen can be obtained by performing B-scan ultrasound examinations. This technique, when applied to radiation therapy, may provide information useful in the accurate placement of treatment ports.

#### METHOD

The ultrasound study is used in addition to standard methods of appraising the limits of the mass. These include: palpation, prior roentgenographic examinations, scintiscans, and localization films obtained with a simulator or the therapy unit itself. We have found it more convenient to perform the ultrasound examination after the estimated port margins have been marked on the patient's skin; however, this may be done in reverse order.

Our equipment consists of a synchronized manual scanner with a 2MHz transducer and a storage type of oscilloscope with an attached camera. Contact scans are obtained in both transverse and longitudinal directions across and beyond the limits of the marked port. When opposing or multiple fields are used, each is examined in this manner.

The margin of the predetermined field is recorded by elevating the transducer from the patient's skin as the skin mark is crossed during the scanning. This will provide a vertical line on the oscilloscope. The number of ultrasonograms obtained depends on the size of the port and the configuration of the mass lesion. If a discrete tumor interface is demonstrated beyond the limits of the original markings, appropriate adjustments are then made. In addition to the morphologic limits of the



Fig. 1. Case 1. Intravenous pyelogram obtained prior to the initiation of radiation therapy. The right kidney is rotated superiorly and displaced medially.

mass, its movement with respiration relative to the field limits can be assessed by direct observation of the oscilloscope at the time of the examination.

#### REPORT OF CASES

Case I. M. B., aged 18 years, was referred to our hospital in March 1967, with a diagnosed malignant thymoma of the anterior mediastinum which was nonresectable. The mass had been detected during the course of a pre-employment physical examination, at which time

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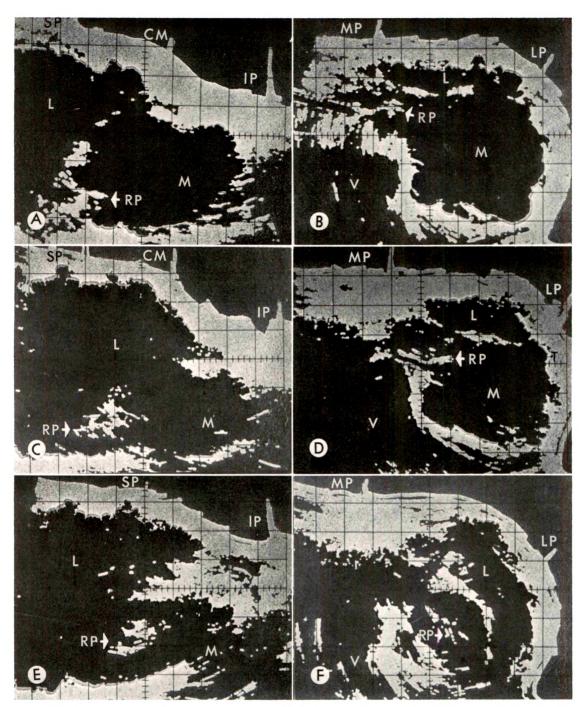


Fig. 2. Case i. (A) Longitudinal ultrasonogram at the horizontal mid port plane (the patient's head to the left). Although the renal outline is not defined sufficiently to separate it from the mass (M), a cluster of echoes from the region of the renal pelvis (RP) is discernible subjacent to the liver (L). The superior and inferior limits of the anterior treatment port are marked (SP and IP) as well as the costal margin (CM). (B) Transverse ultrasonogram at the longitudinal mid port plane (the patient's right to the right). The mass is well displayed in cross section and shown to be separated from the liver edge by an acoustical interface. The renal collecting system echoes, less well defined, are located medially. The medial and lateral limits of the port are marked (MP, LP); vertebral body (V).

(C and D) Ultrasonograms obtained at the same position and electronic gain settings as A and B after I week of radiation therapy, 900 r tumor dose having been delivered. Regression of this radiosensitive mass has already occurred with slight alterations in the relative positions of the kidney and liver.

(E and F) Comparable ultrasonograms obtained after 4 weeks of radiation therapy, 3,150 r tumor dose having been delivered. The mass has almost fully resolved. The renal outline now is almost completely visualized (K). Although irradiation of the kidney could not be avoided initially, the superior port margin was lowered after 1,500 r tumor dose and again at 2,700 r tumor dose to the level of the costal margin.



Fig. 3. Case I. Post-therapy intravenous pyelogram. The right kidney has returned to its normal position.

the patient was asymptomatic and appeared in good health.

A course of irradiation with cobalt 60 was administered to the patient's mediastinum through opposing 12 by 15 cm. anterior and posterior ports. At its conclusion 4,400 r had been delivered to the tumor. During the following 4 months good regression of the mass was documented.

In February 1968 he began to lose weight and developed diarrhea. A mass was then palpated in his epigastrium with roentgenographic evidence of extension to the left upper quadrant. A tumor dose of 3,895 r was delivered to this region through opposing 15 by 18 cm. anterior-posterior ports which were reduced in size after 1,500 r had been delivered. This mass likewise regressed and the patient became asymptomatic.

In May 1967 another mass developed in the right upper quadrant which elevated the right kidney (Fig. 1). In addition, a technetium 99m colloid liver scan demonstrated diminished

activity over the inferior aspect of the liver. At the initiation of further irradiation the port limits were defined in conjunction with both transverse and longitudinal B-scan ultrasonograms (Fig. 2, A and B). The original 15 by 12 cm. opposing fields were reduced in size on 2 occasions during the course of therapy with aid of further ultrasound scans to verify placement and size relative to the rapidly regressing mass (Fig. 2, C-F). At its conclusion 3,150 r had been administered to the tumor, and the kidney returned to a normal position (Fig. 3).

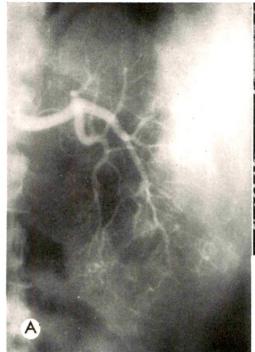
Case II. F.P., male, aged 46 years, had a single episode of hematuria during the latter part of 1968 for which he did not seek medical advice. When low back pain developed in May 1969 he consulted his family physician who detected pyuria and hematuria. The patient was then referred to University Hospitals for further evaluation.

Although the physical examination was negative, a subsequent renal arteriogram displayed a tumor containing abnormal vessels, involving the lower pole of the left kidney (Fig. 4A). This was verified by surgical exploration, with the tissue diagnosis being hypernephroma. Because of extension into the renal hilum, however, the lesion was not resectable. Radiation therapy was then proposed.

Since the lower limit of the mass was not well defined roentgenographically and metallic clips were not placed about the tumor margin at the time of surgery, an ultrasound scan was performed which provided this information. A tumor dose of 4,400 r was subsequently delivered through opposing 15 by 20 cm. ports which were appropriately positioned about the kidney and tumor (Fig. 4B).

Case III. H.D., female, aged 56 years, entered our hospital in February 1969 with a 6 month history of cervical lymphadenopathy associated with night sweats and left abdominal pain. A tender mass was palpated in her left upper quadrant which was consistent with splenomegaly. An exploratory laparotomy was performed at which time an enlarged spleen was removed and a liver biopsy obtained. Follicular lymphoma of mixed cell type was present in both of these organs as well as a cervical lymph node which had been obtained.

Cobalt 60 radiation therapy was administered to both mantle and inverted "Y" fields. After



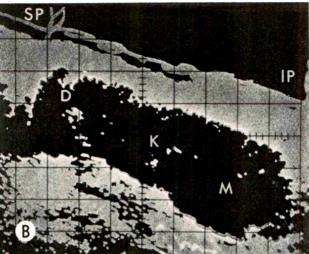


Fig. 4. Case II. (A) Selective left renal arteriogram. Tumor vessels occupy the lower pole of the kidney. The external margin, however, is poorly defined. (B) Longitudinal ultrasonogram at mid port plane (patient's head to the left). The left kidney (K) is defined with the mass expanding its lower pole. The superior margin of the anterior port is above

the level of the diaphragm (D), which was observed to move with respiration at the time of the examination. The inferior port margin clears the lower limit of the gross mass. On this basis a slight inferior adjustment was made.

a midplane dose of 2,100 r had been given the therapy was suspended for I month and then resumed until a final dosage of 3,500 r was delivered.

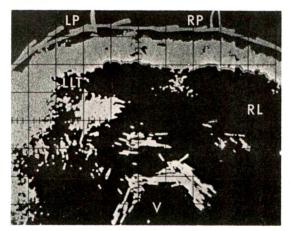


Fig. 5. Case III. Transverse ultrasonogram at the level of the xyphoid (patient's right to the right). The lateral limits of the previous anterior treatment fields are indicated (LP and RP). It can be seen that in addition to the major portion of the right lobe (RL), the tip of the left lobe (LLT) of the liver projected beyond the previous treatment area and therefore had not been irradiated.

Six weeks later she was considered for liver irradiation, but it was difficult to determine exactly what portion of the liver remained unirradiated. However, by marking the limits of the previous port with transverse ultrasonic B-scans, this information was obtained (Fig. 5). Those portions of the liver were then irradiated to a midplane dose of 2,000 r. This was well tolerated by the patient.

#### SUMMARY AND CONCLUSIONS

B-scan ultrasound can be a useful adjunct in the accurate placement of radiation therapy treatment ports in selected cases. In addition to providing information of value in the determination of field size and shape, the display of a lesion's contour in cross section can be of use in the selection of multiple ports for optimal distribution of radiation. In addition, the rate of regression of a neoplasm during and after therapy may be documented.

The technique, however, is limited by the horizontal resolution of the transducer, the presence of good acoustic interfaces at the tumor margin, and the blocking effect of gas within superimposed hollow viscera. Therefore, in many instances little useful information is obtained. However, because pulsed diagnostic ultrasound is innocuous, painless, and easily applied, its continued application and development is justified.

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# LEAK TESTING CHROMATOGRAPHIC RADIUM SOURCES—RADON EMANATION TECHNIQUE\*

By SAMUEL E. CROWDER, B.S. FORT GEORGE G. MEADE, MARYLAND

BECAUSE of the fact that radium 226 has a gaseous decay product, leakage tends to elude wipe testing techniques.

Radon gas escaping from a chromatographic source would, in the main, be exhausted with the carrier gas from the detector exit. Therefore, the environ would be exposed to contamination from the solid decay products of radon before detectable levels of removable activity would accumulate on the detector surface. With small leaks where radium salts are retained and only radon escapes, it seems very possible that measurable levels of contamination will never build up on the detector surface because of the relatively small deposition on the surface and the very brief effective half life of radium A, B, and C deposits which is approximately 30 minutes.1

This situation has required improved techniques for leak testing chromatographic radium sources.

The collection and measurement of radon emanation have been proposed by a number of investigators as a means of leak testing radium sources. Hale<sup>3</sup> utilized charcoal for the collection of radon emanation and, in so doing, placed the source down into the charcoal. This, of course, would favor therapeutic sources such as needles or tubes which are small and can be easily placed in a counting tube.

Unlike therapeutic sources, chromatographic sources are encased in bulky electronic detectors and, therefore, immersion in charcoal is not practical.

In this work the collection and measurement of radon emanation have been adapted as a procedure for leak testing chromatographic radium sources.

#### METHOD

A quantity of activated charcoal consistent with the volume of scintillation detector well is placed in a counting tube fitted with a 2 hole rubber stopper. A tygon tube is inserted and extended down into the charcoal. With chromatograph power off, the tube is attached to the exit line of the detector (Fig. 1).

The carrier gas is allowed to pass through the system for at least 24 hours. The tube is removed, fitted with a solid rubber stopper, allowed to stand 24 hours and counted in a well-type scintillation counter.

The activity may be evaluated with a radium 226 standard. This laboratory utilized a calibrated radium 226 watch

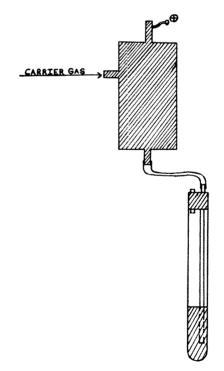


Fig. 1. Charcoal tube attached to detector exit.

<sup>\*</sup> From the Radionuclide Laboratory, First U. S. Army Medical Laboratory, Fort George G. Meade, Maryland.

This material has been reviewed by the office of The Surgeon General, Department of the Army, and there is no objection to its presentation and/or publication. This review does not imply any indorsement of the opinions advanced or any recommendation of such products as may be named.

dial. While the criterion of 0.005 microcuries as the maximum level of contamination prevails, judgement may also be rendered in light of the maximum permissible concentration for radon in air which is  $3\times10^{-8}$  microcuries per cubic centimeter.

#### DISCUSSION AND SUMMARY

In this procedure contamination due to the decay products of escaping radon is readily detected in that the radon is salvaged for ingrowth of daughters. Even with the escape of radium salts, it is likely that contamination will be detected sooner by this technique than by wipe testing the cell surface.

As a basis for presenting counting considerations, a decay scheme of radon is shown in Table 1. In the case of wipe tests the particles of radium A, B, and C are counted and this has to be done immediately after making a wipe because of the brief effective half life of approximately 30 minutes. In this technique the gamma rays of radium B and C² are counted, and whereas the radon daughters are in equilibrium with the parent, the activity has an effective half life of 3.825 days; this allows a longer time for reading samples.

This test may be performed while permitting the detector to remain intact in chromatograph. Removal is not required as may be the case in wipe testing. This offers consolation to many users who experience alteration in chromatograph calibrations in

Table I

DECAY SCHEME OF RADON 222 TO

GAMMA-EMITTING DAUGHTERS

Radioelement	Radiation Emitted	Half Life		
Radon 222	Alpha	3.825 da.		
Polonium 218 (Ra A)	Alpha	3.05 min.		
Lead 214 (Ra B)	Beta, Gamma	26.8 min.		
Bismuth 214 (Ra C)	Beta, Gamma	19.7 min.		

removing a source and would like to leak test without the disturbing detector.

Over-all efficiency in the collection of escaping radon is not known. Nevertheless, because of the distinct advantage in recovering the active deposits of radon, reliability in this technique surpasses that inherent in wipe testing.

Radionuclide Laboratory First US Army Medical Laboratory Fort George G. Meade, Maryland 20755

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# A SYSTEM FOR COMPUTER PROCESSING OF RADIOPHARMACEUTICAL DISBURSEMENT INFORMATION\*

By MARTIN L. NUSYNOWITZ, LTC, MC, WILLIAM A. GOLDSMITH, CPT, MSC, JEROME A. WALISZEWSKI and JOSEPH S. MUSARRA

EL PASO, TEXAS

THE ever expanding medical application of radioactive materials has greatly increased the need for efficient systems for control and monitoring of these radiopharmaceuticals. These controls are necessary for the safety of the professional personnel and patient, compliance with applicable regulations, and efficiency of clinic operation. Any accounting method in a busy clinic can produce a veritable mountain of paperwork, but the digital computer has the capability of eliminating the tedium, improving the accuracy, and reducing the expense associated with manual methods.

The system presented in this paper was developed to fulfill 3 requirements: (1) to record all human uses of radiopharmaceuticals for inventory purposes; (2) to determine workloads; and (3) to maintain a record of radiopharmaceutical dosages to each patient. In addition, this system provides the Radiation Protection Officer with a convenient check of the dose ranges being employed.

#### INPUT DATA

The system was designed in such a manner that the input data could be provided by a technician with a minimum amount of training. Standard 80 character  $3\frac{1}{4} \times 7\frac{3}{8}$  inch cards are punched from a manually prepared form with provision for 80 alphanumeric characters. A sample form showing the data field locations is illustrated in Figure 1. This form indicates that John Z. Smith, born on 1 January 41, received on 30 June 69, for clinical purposes,

I<sup>131</sup> as the iodide in a dose of 49.8 microcuries to perform a thyroidal uptake study and scan. The codes used for the chemical form, and application are shown in Tables I and II. Entries may be expanded as new procedures are instituted. The last letter of the application code shows whether the procedure is a function study (F), imaging or scan procedure (S), or therapy (T).

We chose to use the date of birth in addition to the patient's name as an identification measure, but other means, such as the social security number may be used. The reason for our choice is that the probability of encountering two people with the same full name and date of birth is exceedingly small. Furthermore, almost everyone can provide his date of birth very readily, and this information provides for the computation of the patient's age.

The information on the standard form is punched onto cards for computer processing.

#### THE PROGRAM

The computer program for this system\* was written in Autocoder language for an IBM 1440 System with 4 K core storage. The 2 arrays obtainable with this program are shown in Figures 2 and 3. The type of printout obtained is controlled by the position of a sense switch on the computer console. Figure 2 shows a sample inventory arrayed by radioisotope and chemical form. It may be noted that this printout provides

The mentioning of trade names or manufacturers does not constitute indorsement or approval by the U. S. Government.

\* Copies of the program will be furnished by the authors on request.

\* From the Radioisotope Clinic and Department of Medical Research and Development, William Beaumont General Hospital, El

This material has been reviewed by the office of The Surgeon General, Department of the Army, and there is no objection to its presentation and/or publication. This review does not imply any indorsement of the opinions advanced or any recommendation of such products as may be named.

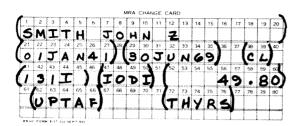


Fig. 1. A sample of the manually prepared form showing the data field locations in brackets.

the total disbursements in microcuries for each chemical form of each radioisotope. The value of this information is readily apparent whenever a human use inventory or an audit of expenditures is required.

An array of radioisotope applications by specific test is shown in Figure 3. This information provides data for the determination of workload and provides the physician with background knowledge about previous tests and dosages which have been administered. Furthermore, this format allows the Radiation Protection Officer to monitor doses administered to patients.

Finally, the punched data cards themselves provide an easily stored and readily accessible permanent record of all human uses of radioisotopes. The printed information on the top line of the card makes reading the card very simple even when filed. These cards are machine sorted alphabetically by patient's name to provide a file for each patient on the amount of

TABLE II
RADIOISOTOPE PROCEDURE ABBREVIATIONS

Chemical Form	of Radioisotope	Symbol
1. Iodide	Approximation (Approximation (Approx	IODI
2. Iodinated Huma	n Serum Albumin	RISA
3. Hippuran		HIPP
4. Rose Bengal		ROSE
5. Triolein		TRIO
6. Oleic Acid		OLEI
7. Cholografin		CHOL
8. Triiodothyronine		$T_3XX$
9. Macroaggregated	Human Serum	**
Albumin		MAAX
10. Soluble Phosphat	te	PHOS
11. Colloidal Phosph	ate	COLL
12. Sodium Chromat	e	NACR
3. Chromic Chloride	2	CRCL
4. Vitamin B-12		$VB_{12}$
5. Ferric Chloride		CHLO
6. Ferrous Citrate		CITR
7. Chlormerodrin (N	Neohydrin®)	NEOH
8. Sulfur Colloid		SCOL
19. Sodium Iothalam	ate (Glofil®)	GLOF

TABLE I
RADIOISOTOPE PROCEDURES

Imaging and Scan Studies		Function Studies	Treatments		
1. Bone	BONES	I. Blood Volume	BLDVF	1. Bone Metastases	BOCAT
2. Brain	BRAIS	2. Body Sodium	BYNAF	2. Cardiac Conditions	CARDT
3. Liver	LIVES	3. Body Water	BYWAF	3. Hyperthyroidism	THYRT
4. Lung	LUNGS	4. Cardiac Output	CARDE	4. Leukemia	LEUKT
5. Pancreas	PANCS	5. Fat Absorption	FTABE	5. Malignant Effusions	EFFUT
6. Pericardial	PERIS	6. Ferrokinetics	FEKIF	6. Polycythemia Vera	PCRVT
7. Renal	RENAS	7. G.I. Blood Loss	GIBDF	7. Thyroid Carcinoma	THCAT
8. Spleen	SPLES	8. G.I. Protein Loss	GIPLF	,,	
9. Thyroid	THYRS	9. Liver Function	LIVEF		
o. Tumor	TUMOS	10. PBI Conversion Ratio	PBICF		
		11. Placenta Localization	PLACE		
		12. Red Cell Survival	SURVE		
		13. Renal Function	RENAF		
		14. Schilling	SCHIF		
		15. T <sub>3</sub>	$T_3XXF$		
		16. Uptake	UPTAF		
		17. Glomerular Filtration Rate	GLFRF		
		18. Renal Blood Flow	REBFF		

radiopharmaceuticals received and the tests performed.

The computer time required for a typical "run" of the program of this system is minimal. We have found that printouts at monthly intervals are convenient. The small cost incurred for computer time is greatly offset by the savings in man hours required by manual methods and the convenience of the records provided.

#### SUMMARY

A system for computer processing of information relative to radiopharmaceutical disbursement is presented. The system conveniently satisfies 3 administrative requirements of any busy radioisotope clinic: (1) preparation of inventories; (2) computation of workloads; and (3) maintenance of patient dosage records.

This system has the potential to be expanded to meet other requirements as they arise.

Martin L. Nusynowitz, LTC, MC Department of Medical Research and Development William Beaumont General Hospital El Paso, Texas 79920

		RADIOIS	RADIOISOTOPE CLINIC 30 APR 70					
NAME	DOB	DATE	ISOTOPE	CHEM	MICROCURIES	USE	TEST	.TEST
BARAJAS ROBERT	17-JAN-43.	21MAR-68	1251	GLOF TOTAL	107.90 107.90	αL	GLFRF	* .
BARAJAS ROBERT DEJESUS GREGORIO	17-JAN-43 24-DEC-17	21 <b>=HA</b> R-68 10-JUL-67	131I 131I	HIPP HIPP TOT <b>AL</b>	78.84 41.15 119.99	CL.	REB FF REMAF	renaf *
DEL ROSARIO Z DELRIO KAREN C GODMAN VIRGINIA R HAIR ROBERT B	20-JAN-29 04-JUN-50 27-JAN-17 19-JUN-30	· 17-NOV-56 04-JAN-68 30-SEP-68 29-JAN-69	1311 1311 1311 1311	1001 1001 1001 1001 TOTAL	40.45 28.52 6000.00 1036.00 7104.97	a a a	UPTAF UPTAF THYRT TUMOS	THYRS
DELEE PAULINE É DELGADO JUAN	11-SEP-94 26-Jun-30	07-APR-67 13-Jun-69	131I 131I	MAAX MAAX TOTAL	158.00 300.30 458.30	ᄄ	LUNGS LUNGS	*
DELOSH ROBERT DOMELL MYRDIA P DRESOM JOHN E HAYES OMELL J	27-FEB-29 22-MAY-19 20-FEB-49 25-JUN-39	07-FEB-67 14-AUG-67 01-DEC-66 18-JAN-68	131I 131I 131I	RISA RISA RISA RISA TOTAL	6.58 716.52 6.66 5.12 734.88	CL CL RD CL	BLDYF BRAIS BLDYF PLACS	CARDF
DINATALE SAM DINATALE SAM	14-MAY-83 14-MAY-93	15-NOY-66 03-NOY-66	131I 131I	ROSE ROSE TOTAL	152.38 38.01 190.39	CL CL	LIVES LIVEF	
VILLESCAS BERTHA J	09-APR-43	22-J <b>AN</b> -68	1311	TRIO TOTAL	99.00 99.00	α	FTABF	•
DEJSUS LEONOR A DELGADO JUAN	11-APR-27 26-JUN-30.	18-JUL-69 13-JUN-69	198AU 198AU	COLL COLL TOTAL	153.06 150.16 303.22	a. a.	LIVES	*
GONZALES ERNESTO	05 <b>-HA</b> Y-11	19-0CT-66	203H6	NEOH Total	160.80 160.80	α	RENAS	•
WIGGINS HELSON C	03~JUL-99	09-FEB-68	32P	PHOS TOTAL	6942.00 6942.00	αL	BOCAT	*
DELOZIER HAROLD L DOLLARD CLYDE A EASLEY JEANE M	07-DEC-26 13-0CT-89 08-JAN-17	14-JAN-70 28-FEB-67 12-DEC-66	51CR 51CR 51CR	NACR NACR NACR TOTAL	29.54 760.65 153.34 343.53	а а	BLDVF SURVF SPLES	*
DIENST LILLIAN H	15-JUN-92.	12- <b>AUG-</b> 68	5700	VB12 TOTAL	0.49 0.49	CL	SCHIF	•
DOMINGUEZ HERIBERTO	18- <b>HA</b> R-10	23- <b>H</b> AY-67	85SR	CHLO TOTAL	100.00 100.00	a.	BOKES	•
DEYAMPERT HORACE	17-JUN-97	26-MAR-70	99HTC	SCOL Total	1090.00 1090.00	CL	LIVES	•
DEMING HOWARD DERAGISCH WILLIAM J	18-FEB-05 13-APR-13	23-APR-68 17-FEB-70	99MTC 99MTC	TC04 TC04 TOTAL	9836.74 9200.00 19036.74	a. a.	BRAIS BRAIS	*

Fig. 2. A sample inventory arranged by radioisotope and chemical form. The cards used for this output were selected to illustrate the flexibility of radioisotope, chemical form, and test. Since these cards were drawn from 4 years' experience with the program, the dates of application (Date column) do not fall within the same quarter as they would in a typical inventory.

RADIOISOTOPE CLINIC 30 APR 70								
KAME.	DOB	DATE	ISOTOPE	CHEM	MICROCURIES	USE	TEST	TEST
DELOSH ROBERT DELOZIER HAROLD L	27-FEB- <b>29</b> 07-DEC- <b>2</b> 6	07-FEB-67 1 <b>4-Jan-7</b> 0	1311 51CR	RISA NACR TOTAL	6.58 29.54 TEST	CT CT	BLDVF BLDVF 2	•
DRESON JOHN E	20-FEB-49	01-DEC-66	131I	RISA TOTAL	6.66 TEST	RD	BL <b>OV</b> F 1	CARDF 1 *
WIGGINS NELSON C	03-JUL- <del>9</del> 9	09-FEB-68	32P	PHOS Total	69 <b>4</b> 2.00 TEST	Œ.	BOCAT 1	•
DOMINGUEZ HERIBERTO	18-MAR-10	23- <b>NA</b> Y-67	85SR	CHLO TOTAL	100.00 TEST	CT.	BO√ES 1	*
DEMING HOWARD DERAGISCH WILLIAM J DOWELL MYRDIA P	18-FEB-05 13-APR-13 22-MAY-19	23-APR-68 17-FEB-70 14-AUS-67	99MTC 99MTC 1311	TCO4 TCO4 RISA TOTAL	9836.74 9200.00 716.52 TEST	a a a	BRAIS BRAIS BRAIS 3	
VILLESCAS BERTHA J	09-APR-43	22-J <b>an</b> -68	1311	TRIO TOTAL	99.00 TEST	CL	FT⊯BF 1	*
BARAJAS ROBERT	17~JAN-43	21 <b>-MA</b> R-68	1251	GLOF Total	107.90 TEST	CL.	GLIRF	*
DINATALE SAM	14-KAY-93	03-NOV-66	1311	ROSE TOTAL	38.01 TEST	CL.	LIVEF 1	*
DELGADO JUAN DEJESUS LEDNOR A DEYAMPERT HORACE DINATALE SAM	26-JUN-30 11-APR-27 17-JUN-97 14-MAY-83	13-JUN-69 18-JUL-69 26-MAR-70 15-NOV-66	198AU 198AU 99MTC 137I	COLL COLL SCOL ROSE TOTAL	150.16 153.06 1090.00 152.38 TEST	а а а	LIVES LIVES LIVES LIVES	*
DELGADO JUAN DELEE PAULINE E	26-JUN-30 11-SEP-94.	13-JUN-69 07-APR-67	131I 131I	MAAX MAAX TOTAL	300.30 158.00 TEST	a. a.	LUNGS LUNGS 2	
HAYES ONELL J	25-JUN-39	8 <del>3-4</del> AL-81	1311	RISA TOT <b>AL</b>	5.12 TEST	α.	PLACS T	*
DEJESUS GREGORIO	24-DEC-17	10-JUL-67	1311	HIPP TOTAL	41.15 TEST	CL.	RENAF 1	*
GONZALES ERNESTO	05 <b>-M</b> AY-11	19-0CT-66	203HG	NEOH Total	160.80 TEST	CL.	RENAS 1	. *
BARAJAS ROBERT	17-J <b>AR-4</b> 3	21-MAR-68	1311	HIPP TOTAL	78.84 TEST	CL	REBFF 1	RENAF
DIENST LILLIAN H	15-JUN-92	12- <b>AUG-</b> 68	5700	VB12 TOTAL	0.49 TEST	α	SCHIF	*
EASLEY JEANE M	08-JAN-17	12-DEC-66	51CR	MACR TOTAL	153.34 TEST	α	SPLES 1	*
DOLLARD CLYDE A	13-0CT-89	28-FEB-67	51CR	NACR Total	160.65 TEST	CL	SUR\F	*
GODMAN YIRGINIA R	27-J <b>AH</b> -17	30-SEP-68	1311	TOTAL	6000.00 TEST	CL.	THYFT	*
HAIR ROBERT B	19-JUN-30	29-JAN-69	1311	TOTAL	1036.00 TEST	a.	TUMOS 1	*
DELRIO KAREN C	04-JUN-50	04-JAN-68	1371	TOOT TOTAL	28.52 TEST	CL.	uptaf 1	*
DEL ROSARIO Z	20-JAN-29	17-NOY-66	1311 Final	IODI TOTAL TOTAL	40.45 TEST TEST	CL.	UPTA= 1 31	THYRS

Fig. 3. A sample inventory arranged by use. The cards used for this output were selected to illustrate the flexibility of radioisotope, chemical form, and test. Since these cards were drawn from 4 years' experience with the program, the dates of application (Date column) do not fall within the same quarter as they would in a typical inventory.



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#### M EDITORIALS M

## FIFTY-THIRD ANNUAL MEETING OF THE AMERICAN RADIUM SOCIETY

THE 53rd Annual Meeting of the American Radium Society will take place at the María Isabel Sheraton Hotel in Mexico City, Mexico, March 15th to March 18th, 1971. This is the first meeting of the Society in Mexico, and prospects for our visit are most exciting.

The Scientific Program Committee has arranged for 3 Symposia concerned with the multidisciplinary approach to cancer management as well as 1 Symposium on immunologic aspects of cancer. This is in context with the theme expressed by the Immediate Past President, Dr. Fernando G. Bloedorn, in his Presidential Address at the 1970 meeting. In addition some 33 compact individual papers on multiple subjects will be presented by the membership.

Three honored foreign members will each take part in a symposium and also present an individual paper as invited guests. These include Sir David Smithers, of Royal Marsden Hospital, London, Professor Hans Ludvig Kottmeier, of Radiumhemmet, Stockholm and Dr. Fernando Gentil of I. C. Hospital, A. C. Camargo, São Paulo, Brazil.

The Janeway Lecture will be delivered by Dr. Lauren V. Ackerman of Washington University, St. Louis. His presentation titled "The Pathology of Radiation Effect in Normal and Neoplastic Tissue" will certainly highlight the scientific program. In addition he will discuss the pathologic aspects of ovarian cancer on one of the symposia.

An innovation in the scientific program will be the first Resident's Prize Award Lecture. The committee for selection of this new addition to the program, under the Chairmanship of Dr. Malcolm Bag-

shaw, is presently deliberating on the submitted articles.

Chairmen of the day for the four morning scientific sessions will include Dr. John V. Blady, President-Elect, Dr. Germán García, Vice-President, Dr. Jerome M. Vaeth, Secretary, and Dr. Antolin Raventos, Treasurer.

Details of the scientific program are published elsewhere in this issue of the Journal.

Dr. José Noriega is Chairman of the Local Arrangements Committee, which includes Dr. Germán García, Dr. Everett Shocket, Dr. Gordon L. Verity and Dr. Bernardo S. del Valle. They have been working diligently to make the meeting a memorable one in our beautiful host city. In conjunction with the Lee Kirkland Group Travel Services, Inc., 3537 Broadway, Kansas City, Mo., tours of the ancient as well as modern landmarks will be arranged. Mr. Kirkland has been designated as the official travel agent for this meeting of the Society and is prepared to answer all inquiries as to travel arrangements to and from North American cities as well as for continuing trips after the meeting. It should be noted that, although no inoculations are necessary, a Mexican Tourist Card is required together with proof of citizenship to travel to Mexico.

The traditional reception by the Radium Chemical Company will again be provided for us at the near-by El Presidente Hotel as one of the features of the social program. The Atomic Energy of Canada, Ltd. has graciously contributed to help in the arrangements of the Society's cocktail party before the Annual Banquet. At the Annual Banquet there will be the Presenta-

tion of the Janeway Medal to Dr. Lauren V. Ackerman and the Past President Certificate to Dr. Fernando G. Bloedorn.

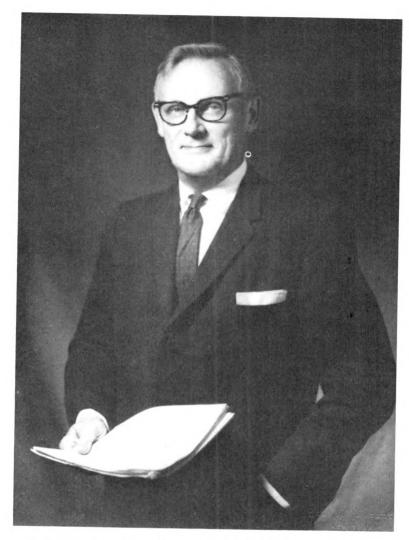
As is the custom, registration is available to all who are interested. Nonmembers will be required to pay a nominal registration fee, and residents in training with adequate proof of status will be registered free.

We are looking forward to a most interesting and rewarding meeting and hope to see you in Mexico.

James F. Nolan, M.D.

President, American Radium Society
Los Angeles Tumor Institute
1407 So. Hope Street
Los Angeles, California 90015





CARL BERNARD LECHNER, M.D. 1908-1970

"NOW I will see if I am a man." So said Carl Bernard Lechner, when he was faced with months of suffering and innumerable operations to attempt to halt a fatal disease. Although he had proved his manhood many times over, his attitude during his illness was unequaled. In a lighter vein he would quip, "Jim, do you think I should start smoking again?"

Born and raised in Erie, his academic

degrees came from Villanova College and Western Reserve University School of Medicine. Internship at St. Vincent Hospital in Erie was followed by three years of general practice. Early interest in Radiology led to a preceptorship under B. Swayne Putts and Ralph D. Bacon, followed by academic training in 1939 and 1940 in the Graduate School of Medicine of the University of Pennsylvania. After four

years in the Army Medical Corps, including service in the European Theatre, Carl rejoined the Radiology group in Erie.

Always willing to serve, he early showed a striking capacity for leadership. Continuing a constructive activity on the hospital medical staffs, in the County Medical Society, the State Medical Society and the Pennsylvania Radiologic Society led to increased responsibility in all these groups which was maintained and at a high level throughout his lifetime. It was logical that his experience as Editor for many years of the Erie County Medical Society "Stethoscope" and of the Pennsylvania Radiologic "Bulletin" should lead to editorship for more than a decade of the Pennsylvania Medical Society "Journal," now PENN-SYLVANIA MEDICINE. Editorials often sharply relevant were frequently reproduced elsewhere. His last editorial for the October, 1970 issue, while urging effective peer review for the medical profession, advanced the case for peer review of legislatures at state and national levels.

Carl had been President of the Erie County Medical Society and of the Pennsylvania Radiological Society. Unable in 1969 to assume presidency of the Pennsylvania Medical Society, he was instead named Honorary President. In addition to membership in local and state medical societies, he was a member of the A.M.A. (Alternate Delegate), as well as of the American Roentgen Ray Society, the Radiological Society of North America, and a Fellow of the American College of Radiology. In Erie, Carl Lechner was a civic leader, particularly in welfare ac-

tivities and serving in his time on the official boards of many agencies and as President of the United Fund, the Erie Arts Council, and the Mercyhurst College Lay Advisory Board.

Friendly, knowledgeable and talented, he made full use of these qualities in the care of patients, in behalf of organized medicine and of society. In the funeral address his friend, Bishop Alfred Watson, called attention to his loyalty, his integrity and his courage, all of which were manifested in his every activity at home, in the office and wherever he was in contact with others. It can be said that he professed and practiced his religion every day.

Tennis, as allowed by weather and schedule, was a principal and major interest. Books were truly a hobby with a wide interest in the classics as well as in current literature. He lived and used affectionately in speech and print the English language and the American idiom. Although not a musician, his love of classical music was strong and fulfilled in part by attendance at concerts and musical affairs. Blessed with an understanding wife with musical talent and with a daughter and three sons who, also, like good music, he always found music available at home from the piano or at the turntable.

To members of the immediate family and many other relatives, close friends and associates, Carl Lechner's life and works will always be a reason for faith and effort. "Peace."

JAMES JACKMAN, M.D.

105 Professional Building Erie, Pennsylvania 16501



#### THE AMERICAN RADIUM SOCIETY

#### FIFTY-THIRD ANNUAL MEETING

# MARIA ISABEL SHERATON HOTEL MEXICO CITY MARCH 15-18, 1971

Monday, March 15, 1971

Opening Session 8:00 A.M.-I:00 P.M.

Welcome Address

President's Address. James F. Nolan, M.D., Los Angeles, Calif.

John V. Blady, M.D., Philadelphia Pa., Presiding

Symposium: The Immunologic Aspects of Malignant Disease.

William E. Powers, M.D., St. Louis, Mo., Moderator

#### Participants

Herman D. Suit, M.D., Houston, Tex. Ralph E. Johnson, M.D., Bethesda, Md. Alfred S. Ketcham, M.D., Bethesda, Md.

Multidisciplinary Approach to the Management of Patients with Testicular Tumors. Sir David W. Smithers, London, England.

Advanced Ovarian Cancer; Therapy with Radiation and Cyclophosphamide in a Random Series. Carl E. Johnson, M.D., David G. Decker, M.D., and Martin Van Herik, M.D., Rochester, Minn.

External Pelvic Irradiation as a Preoperative Surgical Adjuvant in the Treatment of Carcinoma of the Endometrium. J. A. del Regato, M.D., and C. M. Chahbazian, M.D., Colorado Springs, Colo. Hydatidiform Moles in Hawaii. W. J. Natoli, M.D.,

Honolulu, Hawaii.

The Role of Lymphangiography in the Diagnosis and Treatment of Malignant Testicular Turnors. John G. Maier, M.D., and Dean T. Schamber, M.D., Washington, D.C.

Carcinoma of the Female Urethra. Charles H. Taggart, M.D., Joseph R. Castro, M.D., and Felix N. Rutledge, M.D., Houston, Tex.

Daily Hybaroxic Radiotherapy; Evaluation of Ninety-Six Patients. Henry L. Jaffe, M.D., and A. Robert Kagan, M.D., Los Angeles, Calif.

Hyperbaric Oxygen Radiation Therapy; Review of Controlled Studies in the World Experience and at the Radiation Center, L.D.S. Hospital. Henry P. Plenk, M.D., Salt Lake City, Utah.

Conservative Surgery Following Preoperative Radiotherapy of Lung Cancer. V. Saxena, M.D., Frank R. Hendrickson, M.D., and R. Jensik, M.D., Chicago, Ill.

The Role of Radiotherapy and Chemotherapy in the

Surgical Management of Pulmonary Metastases. Alan Turnbull, M.D., and John L. Pool, M.D., New York, N.Y.

Indications and Complications of Major Surgery after Radical Radiotherapy. Sameer Raffa Demetrious, M.D., Brooklyn, N.Y.

Tuesday, March 16, 1971

9:00 A.M.-I:00 P.M.

Germán García, M.D., Mexico City, Mex., Presiding

Symposium: Multidisciplinary Approach to Colorectal Cancer.

Morton Kligerman, M.D., New Haven, Conn., Moderator.

#### Participants

Clifford Allen, M.D., Portland, Ore. Fernando Gentil, M.D., São Paulo, Brazil.

Cancer of the Endometrium with Special Regard to Radiotherapy. Hans Ludvig Kottmeier, M.D., Stockholm, Sweden.

Radiation Protection. Herbert Parker, F. Inst. P., Richland, Wash.

Afterloading Systems in the Treatment of Malignant Disease. Morton Simon, M.D., New York, N.Y.

Radiation Injuries of the Stomach, Small Bowel and Colon. Bernard Roswit, M.D., Stanley J. Malsky, Ph.D., and Cyprian B. Reid, B.Sc., Bronx, N.Y.

Dosimetric Consideration in the Interstitial Use of Encapsulated Iodine 125 Sources. J. G. Holt, A. P. Pinkerton, J. S. Laughlin, Ph.D., and B. S. Hilaris, New York, N.Y.

#### Janeway Lecture

Lauren V. Ackerman, M.D., St. Louis, Mo.

Wednesday, March 17, 1971

9:00 A.M.-I:00 P.M.

Jerome M. Vaeth, M.D., San Francisco, Calif., Presiding

Symposium: Multidisciplinary Approach to Lymphoma.

Henry S. Kaplan, M.D., Stanford, Calif., Moderator.

#### Participants

Sir David W. Smithers, London, England.

Cancer of the Penis. Fernando Gentil, M.D., São Paulo, Brazil.

A Study of Anatomy and Dosimetry in the Treatment of Carcinoma of the Uterus. V. P. Collins, M.D., M. Peterson, D.S., John Wall, M.D., and Gaynor Janes, M.D., Houston, Tex.

An Integrated Radiotherapy System. F. W. George, M.D., H. L. Frey, M.D., D. L. Neblett, B.E., and H. R. Haymond, Ph.D., Los Angeles, Calif.

Matrix Dosimeter for High Energy Radiotherapy Machines. H. E. Johns, Ph.D., and W. B. Taylor, Toronto, Canada.

Emotional Reactions to Having Cancer. Arthur Peck, M.D., New York, N.Y.

Carcinoma of the Cervix in a Latin American Community. Victor A. Marcial, M.D., San Juan, Puerto Rico.

Extended Field Therapy for Squamous Cell Carcinoma of the Uterine Cervix. Gilbert H. Fletcher, M.D., Houston, Tex.

Hypogastric Artery Infusion and Radiation Therapy for Advanced Squamous Cell Carcinoma of the Cervix. Julian P. Smith, M.D., George E. Randall, M.D., Felix Rutledge, M.D., Robert D. Lindberg, M.D., Joseph R. Castro, M.D., and Gilbert Fletcher, M.D., Houston, Tex.

Resident's Prize Award Lecture

Installation of Officers

Thursday, March 18, 1971

9:00 A.M.-I:00 P.M.

Antolin Raventos, M.D., Davis, Calif., Presiding

Symposium: Multidisciplinary Approach to Carcinoma of the Ovary.

A. N. Arneson, M.D., St. Louis, Mo., Moderator.

#### **Participants**

Hans Ludvig Kottmeier, M.D., Stockholm, Sweden Lauren Ackerman, M.D., St. Louis, Mo. Felix N. Rutledge, M.D., Houston, Tex. Carlos Perez, M.D., St. Louis, Mo.

Radiotherapy of Orbital Tumors. José Noriega,

M.D., Mexico City, Mex.

The Management of the Patient with Retinoblastoma. Ronald Thompson, M.D., and Justin J. Stein, M.D., Los Angeles, Calif.

Cure of Orbital Rhabdomyosarcoma by Radiation Therapy. Robert H. Sagerman, M.D., Patricia Tretter, M.D., and Robert M. Ellsworth, M.D., Syracuse, N.Y.

Combined Therapy in Advanced Head and Neck Cancer. F. F. Gollin, M.D., F. J. Ansfield, M.D., G. Ramirez, M.D., and H. Vermund, M.D., Madison, Wisc.

Long Term Results of Treatment of Chemodectomas of the Glomus Jugulare. Philip M. Hatfield, M.D., A. Everett James, M.D., and Milford D. Schulz, M.D., Boston, Mass.

The Therapeutic Problem of Metastatic Neck Adenopathy. Juan V. Fayos, M.D., and Isadore

Lampe, M.D., Ann Arbor, Mich.

The Role of Radiotherapy and of Surgery in the Management of Localized Epidermoid Carcinoma of the Maxillary Sinus. Samuel S. Kurohara, M.D., James P. Fitzgerald, M.D., Ahmed O. Badib, M.D., and John H. Webster, M.D., Los Angeles, Calif.

Malignant Tumors of the Tonsil; Analysis of Failures and Factors Affecting Prognosis. C. A. Perez, M.D., L. V. Ackerman, M.D., W. B. Mill, M.D., J. H. Ogura, M.D., and W. E. Powers, M.D., St. Louis, Mo.

Sweat Gland Carcinoma Arising in Irradiated Skin. Ali A. El-Domeiri, M.D., Andrew G. Huvos, M.D., and Edward J. Beattie, Jr., M.D., New York, N.Y.

Hodgkin's Disease and Other Lymphomas Treated with Radiation Therapy; Followup Data and the Value of Laparotomy in Diagnosis and Treatment. Leonard R. Prosnitz, M.D., James J. Fischer, M.D., Raul Vera, M.D., and Morton M. Kligerman, M.D., New Haven, Conn.

Integrated Therapy for Ewing's Sarcoma. Ralph E. Johnson, M.D., and Thomas C. Pomeroy, M.D.,

Bethesda, Md.

High Dose, Preoperative Supervoltage Irradiation for Osteogenic Sarcoma. R. Lewis Royster, M.D., E. Richard King, M.D., J. H. Ebersole, M.D., and S. H. Levitt, M.D., Bethesda, Md.



#### **NEWS ITEMS**

#### CONFERENCE ON AFTERLOADING IN RADIOTHERAPY

A conference on Afterloading in Radiotherapy will be held at the Mount Sinai School of Medicine in New York, May 6–8, 1971.

Distinguished speakers from the United States and abroad will present the status of brachytherapy with afterloading and re-

mote loading techniques.

The conference is co-sponsored by the Bureau of Radiological Health of The United States Department of Health, Education and Welfare, The Radiotherapy Department of the Mount Sinai School of Medicine and The Page and William Black Postgraduate School of Medicine. Attendance will be limited.

For application forms and further information, write to the Registrar, Page and William Black Postgraduate School of Medicine, Fifth Avenue & 100th Street, New York, New York 10029.

### SYMPOSIUM ON POLYTOMOGRAPHY OF THE TEMPORAL BONE

The third two-day Symposium on Polytomography of the Temporal Bone will be given under the auspices of the Wright Institute of Otology at Community Hospital, Indianapolis, Indiana, on March 6 and 7, 1971.

Subjects covered are "Basic Anatomy of the Temporal Bone" and "Technique of Polytomography of the Temporal Bone" with demonstration of normal tomograms. Pathologic conditions revealed by polytomography, such as cholesteatoma, ossicular chain problems, otosclerosis, fractures, foreign bodies, tumors, and congenital anomalies will be shown on original tomograms and the clinical applications will be discussed.

The number of registrants is limited to 15.

Inquiries should be directed to: Wright

Institute of Otology, Community Hospital, 1500 North Ritter Avenue, Indianapolis, Indiana 46219.

#### COLUMBIA-PRESBYTERIAN MEDICAL CENTER

Postgraduate Course in Neuroradiology

The Department of Radiology, College of Physicians and Surgeons, Columbia University, announces a postgraduate course in Neuroradiology to be held at the Columbia-Presbyterian Medical Center, May 3-7, 1971.

The course is a comprehensive review of diagnostic neuroradiology and is designed primarily for radiologists, neurologists and

neurological surgeons.

Emphasis will be placed on basic information used frequently in neuroradiologic diagnosis, especially angiography. Topics of the course will also include plain film diagnosis, pneumography, myelography, radiology of the orbits, the use of radioactive isotopes and neuroradiologic approaches to the solution of specific clinical problems.

Inquiries should be addressed to the Program Director, Ernest H. Wood, M.D., Neurological Institute of New York, 710 West 168th Street, New York, New York 10032.

#### RADIATION RESEARCH SOCIETY

The 19th Annual Meeting of the Radiation Research Society will be held in Boston, Mass., at the Statler Hilton Hotel, May 9-13, 1971.

The preliminary plans include a major plenary session sponsored by the Late Effects Group on the current status of the knowledge of human effects of low doses of radiation, and major symposia on primary chemical species, macromolecular effects, cell renewal systems, and tritium.

For further information please contact

Richard J. Burk, Jr., Executive Secretary, Radiation Research Society, 4211 39th Street, N.W., Washington, D.C. 20016.

#### CHEST RADIOLOGY

This postgraduate course in chest radiology is organized by the Department of Radiology of the Albert Einstein College of Medicine and its affiliated hospitals, and will be held May 17-21, 1971.

The course is intended for radiologists and other physicians interested in diseases of the chest. Attention will be directed toward the practical aspects of specialized diagnostic procedures as well as to a comprehensive review of the present day concepts of radiology of the respiratory tract. Film interpretation panels will emphasize the approach to diagnostic problems.

The Program Chairmen are: Milton Elkin, M.D., Professor and Chairman, Department of Radiology, Albert Einstein College of Medicine; and Harold G. Jacobson, M.D., Professor of Radiology, Albert Einstein College of Medicine, and Radiologist-in-Chief, Montefiore Hospital and Medical Center.

The Place is Robbins Auditorium, Albert Einstein College of Medicine, Eastchester Road & Morris Park Avenue, Bronx, New York.

The Guest Faculty comprises: David H. Baker, M.D., Walter E. Berdon, M.D., Benjamin Felson, M.D., Robert G. Fraser, M.D., E. Robert Heitzman, M.D., George Jacobson, M.D., Averill A. Liebow, M.D., Leo G. Rigler, M.D., Irving J. Selikoff, M.D., Robert E. Steiner, M.D., and Elias G. Theros, M.D.

Application for registration should be forwarded to Milton Elkin, M.D., Program Chairman, Albert Einstein College of Medicine, Bronx, New York 10461.

#### FELLOWSHIP IN RADIOLOGICAL SCIENCE AND NUCLEAR MEDICINE

The Donner Laboratory, University of California, announces an opportunity for advanced study and research in radiological science and nuclear medicine.

Activities include investigation of the biological effects of high-energy, heavy particles, fast neutrons and pi mesons, participation in the use of high-energy particles in therapy, and the diagnostic, therapeutic, and investigative uses of radioisotopes.

One or two courses in the graduate program in biophysics and medical physics may be taken concurrently.

Applicants should have had residency training in radiology. Stipend will be made available from a training grant, or the laboratory will sponsor the individual's application for a direct fellowship.

Application forms are available from: John H. Lawrence, M.D., Donner Laboratory, University of California, Berkeley, California 94720.

#### THE AMERICAN SOCIETY OF RADIOLOGIC TECHNOLOGISTS

This year The Louisiana Society of Radiologic Technologists will have the honor of hosting the 43rd Annual Meeting of The American Society of Radiologic Technologists in New Orleans, at the Jung Hotel, July 10-15, 1971.

It is anticipated that this will be the greatest annual meeting that The American Society of Radiologic Technologists has ever held. An outstanding program is prepared.

For further information please contact Mary E. Smith, R.T. (ARRT), Chairman, Publicity Committee, Desire Medical Center, 2630 Desire Street, New Orleans, Louisiana 70117.



#### **BOOK REVIEWS**

Golden's Diagnostic Radiology. Section 5: Digestive Tract. Edited by Laurence L. Robbins, Clinical Professor of Radiology, Harvard Medical School; Radiologist-in-Chief, Massachusetts General Hospital, Boston, Mass., with Ross Golden, Christian V. Cimmino, Lois C. Collins, Jack R. Dreyfuss and Murray L. Janower. Cloth. Pp. 942, with many illustrations. Price, \$41.50. The Williams & Wilkins Company, 428 East Preston Street, Baltimore, Md. 21202, 1969.

This book consisting of 942 pages is authored by Drs. Golden, Cimmino, Collins, Drayfuss and Janower. It is part of the Golden's Diagnostic Radiology. The book is a good introduction to gastrointestinal radiology but, like many multi-authored books, suffers from unevenness in concepts, text, emphasis and quality of illustrations. Some sections are superbly written and very well illustrated, such as the Section on the Esophagus; others dwell on minutiae and spend considerable space on concepts that were in vogue in the 1930s but have long been abandoned, one example being "Chronic Hypertrophic Gastritis."

Some of the illustrations, also apparently from the 1930s with photographic detail, are out of place in a contemporary textbook. The Section on the Colon is well organized and al-

though short is fairly complete.

In the Section on Technique, this reviewer feels—perhaps without justification—that the failure to include the water enema for diagnosis of lipomas and arteriography for demonstration of the site of massive bleeding into the colon is a serious omission. It is surprising that, along with the many excellent illustrations, many films of barium enema examinations are underexposed, permitting no penetration through the barium column.

In spite of these criticisms, there is much good material in this book. Its value to the reader would have been even greater if the coverage, illustrations, and references were of more even quality.

ALEXANDER R. MARGULIS, M.D.

RADIOLOGIC EXAMINATION OF THE COLON.
This book is an overprint of the final portion of Section 5: "The Digestive Tract" from

Golden's Diagnostic Radiology. By Jack R. Dreyfuss, M.D., Assistant Clinical Professor of Radiology, Harvard Medical School; Radiologist, Massachusetts General Hospital, Boston, Mass.; and Murray L. Janower, M.D., Assistant Professor of Radiology, Harvard Medical School; Associate Radiologist, Massachusetts General Hospital, Boston, Mass. Cloth. Pp. 125, with many figures. Price, \$9.75. The Williams & Wilkins Company, 428 East Preston Street, Baltimore, Md. 21202, 1969.

This short, concise book on "The examination of the colon" is very well organized, beautifully written, and more complete than one would expect of a book this size. The bibliography is well selected and shows judicious discrimination. This work is a section of the 5th volume on "Examination of the Gastrointestinal Tract" in Golden's Diagnostic Radiology. It would have been a good idea, however, if the editors had thought of re-numbering the pages so they would not start with page 5-801 and the illustrations with the remarkable photograph number 502.

In the Section on Technique, a few more available techniques could have been mentioned, notably the use of selective arteriography for localization of massive arterial bleeding into the colon; perhaps for completeness sake, the water enema could also have been mentioned. Such small omissions, however, do not subtract from the basic value of this book which is an excellent introduction to radiology

of the colon for beginning residents.

It is disappointing that, with so many beautiful illustrations, particularly the excellent reproduction of many specimens, plain roentgenograms and double contrast studies, the conventional barium enema films were obtained with low kilovoltage technique and, therefore, do not have the detail one would expect.

ALEXANDER R. MARGULIS, M.D.

#### **BOOKS RECEIVED**

THE INTERVERTEBRAL DISC. By Anthony F. De-Palma, M.D., Professor of Orthopedic Surgery, Jefferson Medical College, Thomas Jefferson University; and Richard H. Rothman, M.D., Ph.D., Associate Professor of Orthopedic Surgery, Jef-

ferson Medical College, Thomas Jefferson University. Cloth. Pp. 373, with 243 illustrations. Price, \$16.50. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. 19105, 1970.

SURGICAL ONCOLOGY. Edited by Frédéric Saegesser and Jacques Pettavel. Current Problems in Surgery: 14. Cloth. Pp. 908, with 212 illustrations. Price, Fr. 198.—. Hans Huber Publisher, Marktgasse 9, 3000 Bern 7, Switzerland, 1970.

The Immunology of Malignant Disease. By Jules E. Harris, M.D., F.R.C.P.(C), F.A.C.P., Assistant Professor of Medicine, University of Ottawa, Ottawa, Canada; formerly Assistant Professor of Medicine, Department of Developmental Therapeutics, University of Texas, M. D. Anderson Hospital and Tumor Institute, Houston, Texas; and Joseph G. Sinkovics, M.D., F.A C.P., Associate Professor of Medicine and Chief, Section of Clinical Tumor Virology and Immunology, Department of Medicine, University of Texas, M. D. Anderson Hospital and Tumor Institute, Houston, Texas. Cloth. Pp. 251. Price, \$15.00. C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. 63103, 1970.

Mammography and Breast Diseases. By Robert L. Egan. Section 19: Golden's Diagnostic Radiology. Laurence L. Robbins, Editor. Cloth. Pp. 272, with many illustrations. Price, \$18.∞. Williams & Wilkins Company, 428 East Preston Street Baltimore Md. 2122, 1070.

Street, Baltimore, Md. 21202, 1970.

X-RAY TECHNOLOGY EXAMINATION REVIEW BOOK. Volume 2. Second edition. Edited by William O. Crawford, Jr., M.D., Assistant Professor of Radiology, Yale University School of Medicine, Yale University, New Haven, Conn.; and Richard A. Strother, R.T., A.R.R.T., Chief Technologist, Department of Radiology, Georgetown University Hospital, Washington, D. C. Paper. Pp. 192. Price, \$7.00. Medical Examination Publishing Co., Inc., 65–36 Fresh Meadow Lane, Flushing, N. Y. 11365, 1970.

Indications and Alternatives in X-Ray Diagnosis. By Melvyn H. Schreiber, M.D., Professor of Radiology, University of Texas Medical

Branch, Galveston, Texas. Paper. Pp. 117. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill. 62703, 1970.

Pädiatrische Neuroradiologie. By Von Kurt Decker, and Herbert Backmund. Cloth. Pp. 193, with 159 figures. Price, DM 79.-. Georg Thieme Verlag, Stuttgart. In U.S.A. and Canada, Intercontinental Medical Book Corporation, New York, N. Y. 10016, 1970.

BIOLOGY OF THE IMMUNE RESPONSE. By Peter Abramoff, Ph.D., Professor and Chairman, Department of Biology, Marquette University; and Mariano F. La Via, M.D., Professor of Pathology, The Bowman Gray School of Medicine, Wake Forest University. Cloth. Pp. 492, with some illustrations. Price, \$12.95. McGraw-Hill Book Company, 330 West 42nd Street, New York, N. Y. 10036, 1970.

The Acute Abdomen in Infancy and Childhood. By John G. Raffensperger, M.D., Associate Professor of Surgery, University of Illinois College of Medicine; Division Head, General Surgery, The Children's Memorial Hospital, Chicago, Ill.; Ruth Andrea Seeler, M.D., Assistant Professor of Pediatrics, University of Illinois College of Medicine; Pediatric Hematologist, Cook County Children's Hospital, Chicago, Ill.; and Rogelio Moncada, M.D., Professor of Radiology, Director of Education, Department of Radiology, Loyola University of Chicago. Cloth. Pp. 130, with many figures. Price \$12.00. J. B. Lippincott Company, East Washington Square, Philadelphia, Pa. 19105, 1970.

VITAMIN D AND SKELETAL METABOLISM: EXPERIMENTAL STUDIES IN THE RAT. By J. A. Sevastikoglou, M.D., R. D. Ray, M.D., Ph.D., S.-O. Hjertquist, M.D., and E. Bergquist, M.D. Paper. Pp. 85, with some figures. Acta Orthopaedica Scandinavica, Supplementum No. 136. Munksgaard, Copenhagen, 1970.

MEASUREMENT OF STABILITY OF TIBIAL FRACTURES: A MECHANICAL METHOD. By Acke Jernberger. Paper. Pp. 88, with some figures. Acta Orthopaedica Scandinavica, Supplementum No. 135.

Munksgaard, Copenhagen, 1970.



#### SOCIETY PROCEEDINGS

#### MEETINGS OF RADIOLOGICAL SOCIETIES\*

#### United States of America

American Roentgen Ray Society Secretary, Dr. Ted F. Leigh, Emory University Clinic,

Atlanta, Ga. 30322. Annual meeting: Sheraton Hotel, Boston, Mass., September 28-October 1, 1971. American Radium Society

Secretary, Dr. Jerome M. Vaeth, Saroni Tumor Institute, 1600 Divisadero St., San Francisco, Calif. 94115. Annual meeting: Mexico City, Mexico, March 15-18, 1971.

RADIOLOGICAL SOCIETY OF NORTH AMERICA Secretary-Treasurer, Dr. Maurice Doyle Frazer, 1744 South Fifty-eighth St., Lincoln, Neb. Annual meeting: Palmer House, Chicago, Ill., November 28-December 3,

AMERICAN COLLEGE OF RADIOLOGY

Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill. Annual meeting: St. Louis, Mo., Chase-Park Hotel, March 30-April 3, 1971.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION Secretary, Dr. Ted F. Leigh, Emory University Clinic,

Secretary, Dr. Ted F. Leigh, Emory University Clinic, Atlanta, Ga., 30322. Annual meeting: Atlantic City, N. J., June 20–24, 1971.

American Board of Radiology Secretary, Dr. C. Allen Good. Correspondence should be directed to Kahler East, Rochester, Minn. 55901.

Oral examinations will be held in the following cities during the next 2 years: Bal Harbour, Fla., June 7–11, 1971, Americana Hotel; Dallas, Tex., Dec. 6–10, 1971, Statler-Hilton Hotel; Washington, D.C., June 5–9, 1972, Washington-Hilton Hotel; and Atlanta, Ga., Dec. 4–8, 1972. Sheraton-Biltmore Hotel.

1972, Sheraton-Biltmore Hotel.
Written examinations are scheduled in June of each

year in 13 large centers, and applications must be received in the Board Office before Sept. 30 of the year preceding the one in which the candidate wishes to be

Deadline for filing applications for any examination

in 1972 is September 30, 1971. American Association of Physicists in Medicine Secretary, Leonard Stanton, Hahnemann Medical College, 230 N. Broad St., Philadelphia, Pa. 19102. Armual meeting to be announced.

American Society of Therapeutic Radiologists Secretary, Dr. Carl R. Bogardus, Jr., University of Oklahoma Medical Center, Oklahoma City, Oklahoma 73104

AMERICAN INSTITUTE OF ULTRASOUND IN MEDICINE

Secretary, F. J. Fry, M.Sc., Bioacoustics Lab., University
of Illinois, Urbana, Ill.

AMERICAN SOCIETY OF NEURORADIOLOGY

Secretary-Treasurer, Dr. Eugene V. Leslie, Edward J. Meyer Memorial Hospital, 462 Grider St., Buffalo, N. Y.

THIRTEENTH INTERNATIONAL CONGRESS OF RADIOLOGY Meeting: Madrid, Spain, Oct. 13-19, 1973. TENTH INTER-AMERICAN CONGRESS OF RADIOLOGY

Counselor for the United States, Dr. Manuel Viamonte, Jr., University of Miami School of Medicine, Jackson Memorial Hospital, Miami Fla. 33136. President, Dr. Victor A. Marcial, Puerto Rico Nuclear Center, Caparra Heights Station, San Juan, Puerto Rico

Meeting: San Jeronimo-Hilton Hotel, San Juan, Puerto Rico, May 16-22, 1971.

INTER-AMERICAN COLLEGE OF RADIOLOGY President, Dr. Juan A. del Regato, Penrose Cancer Hospital, 2215 North Cascade Ave., Colorado Springs, Colo. FIRST ASIAN AND OCEANIAN CONGRESS OF RADIOLOGY Honorary Secretary, Dr. J. J. Martin, Box 805 F., G.P.O., Melbourne, 3001, Australia. Meeting: Melbourne, Australia, Nov. 22–26, 1971.

ALABAMA CHAPTER OF ACR

Secretary, Dr. William V. Weldon, Medical Arts Building, Birmingham, Ala. 35205. Meets time and place of Alabama State Medical Association.

Alaska Radiological Society

Secretary, Dr. Bruce C. Wright, Providence Hospital, Anchorage, Alaska. Meets third Wednesday each month. ARIZONA RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary, Dr. Wesley S. Fee, 2421 E. 6th St., Tucson, Ariz. 85719. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

ARKANSAS CHAPTER OF ACR

Secretary Treasurer, Dr. Wilma C. Diner, Univ. of Arkansas Medical Center, Little Rock, Ark. 72201. Meets twice annually, the Spring Meeting being in conjunction with and at the place of the State Medical Association. Association of University Radiologists

Secretary-Treasurer, Dr. Elliott C. Lasser, University Hospital of San Diego County, San Diego, Calif. 92103. Annual Meeting: Durham, N. C., May 13–15, 1971, with the Duke University and University of North Carolina Radiology Departments serving, as co-hosts.

ATLANTA RADIOLOGICAL SOCIETY Secretary, Dr. Richard S. Colvin, Emory University Clinic, Atlanta, Ga. 30322. Meets on four Thursday evenings during the academic year at a time announced in early September of each year, at the Academy of Medicine, Atlanta, Ga., at 8:∞ г.и.

BAVARIAN-AMERICAN RADIOLOGIC SOCIETY Advisor, Colonel Paul E. Sieber. Secretary, LTC Peter B. Riesz, USAH Bad Cannstatt, APO 09154, New York, N. Y. Meets quarterly.

BLOCKLEY RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. R. John Gould, 41 Lombardy Rd., Drexel Hill, Pa. 19026.

BLUEGRASS RADIOLOGICAL SOCIETY

Secretary-Treasurer, Joseph A. Sayeg, Ph.D., Radiation Physicist, University of Kentucky, Lexington, Ky. 40506. The Society meets once each month during the school year.

BRONX RADIOLOGICAL SOCIETY, NEW YORK STATE, CHAP-TER ACR

Secretary-Treasurer, Dr. David Bruce Hayt, 600 E. 233rd St., Bronx, N. Y. 10466. Meets 4 times a year.

Brooklyn Radiological Society

Secretary-Treasurer, Dr. Rubem Pochaczevsky, 300 Skillman Ave., Brooklyn, N.Y. 11211. Meets first Thursday of each month, October through June.

BUFFALO RADIOLOGICAL SOCIETY

Secretary, Dr. Glen M. Ebersole, 405 Spring St., Jamestown, N.Y. 14701. Meets second Monday evening each month, October to May inclusive, at University Club. CALIFORNIA RADIOLOGICAL SOCIETY, CALIFORNIA CHAPTER

Secretary-Treasurer, Dr. John L. Gwinn, Childrens Hospital of Los Angeles, P.O. Box 54700, Los Angeles, Calif.

CATAWBA VALLEY RADIOLOGICAL SOCIETY

Secretary, Dr. Emmett R. White, P. O. Box 10, Rutherford College, N. C. 28671. Meets every Thursday, Dept. of Radiology, Valdese General Hosp., Valdese, N. C., at 12:30 P.M.

<sup>\*</sup> Secretaries of societies are requested to send timely information promptly to the Editor.

CENTRAL NEW YORK RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. David N. Cheris, Community General Hospital of Greater Syracuse, Broad Road, Syracuse, N. Y. 13215. Meets first Monday each month

October through May.
CENTRAL OHIO RADIOLOGICAL SOCIETY

Secretary, Dr. James V. Blazek, 2586 Lane Rd., Columbus, Ohio 43220. Meets second Thursday in October, November, January, and March 15, and May 19 at Fort Hayes Hotel, Columbus, Ohio.

CHICAGO ROBNTGEN SOCIETY

Secretary-Treasurer, Dr. William T. Moss, 250 E. Superior St., Chicago, Ill. 60611. Meets third Thursday of each month, October to April, except December, at the Bismarck Hotel, Chicago, Ill.

CLEVELAND RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Daniel E. Wertman, 11311 Shaker Blvd., Cleveland, Ohio 44104. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and April.

COLORADO RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Marvin L. Daves, Univ. of Colorado Medical Center, 4200 E. Ninth Ave., Denver, Colo. 80220. Meets third Friday of each month at Denver Athletic Club from September through May.

CONNECTICUT VALLEY RADIOLOGIC SOCIETY
Secretary, Dr. William W. Walthall, Jr., 130 Maple St.,

Springfield, Mass. Meets in April and October.

DALLAS-FORT WORTH RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. V. V. Kirby, 1722 Spring Lake Dr., Arlington, Tex. 76010. Meets the 3rd Monday of every month at 6:30 P.M., at the Cibola Inn, Arlington, Tex.

DELAWARE CHAPTER OF ACR

Secretary, Dr. James H. Taylor, Wilmington Medical Center, Wilmington, Del. 19899. EAST BAY RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. S. Walter Kran, Doctors' Hospital of San Leandro, 13855 East 14th St., San Leandro, Calif. 94578. Meets first Thursday each month, Oct. through May, at University Club, Oakland, Calif.

EAST TENNESSEE RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Eberhard F. Besemann, Baroness Erlanger Hospital, Chattanooga, Tenn. 37403.

Meets in January and September.

FLORIDA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Wm. F. Lindsey, 1215 Hodges Dr., Tallahassee, Fla. 32303. Meets twice annually, in the spring with the annual State Society Meeting and in the fall.

FLORIDA WEST COAST RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Allen L. Sheer, University Community Hospital, 13505 N. 31st St., Tampa, Fla. 33612. Meets in January, March, May, July, September

and November.

GEORGIA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Walker Harris, The Medical Center, Columbus, Ga. 31902. Meets in spring and fall at Annual State Society Meeting.
GREATER CINCINNATI RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Owen L. Brown, 2421 Auburn Ave., Cincinnati, Ohio 45219.

GREATER LOUISVILLE RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. L. D. LeNeave, 315 E. Broadway, Louisville, Ky. 40202. Meets monthly.

GREATER MIAMI RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. John Kathe, North Shore Hospital, Miami, Fla. 33150. Meets monthly, third Wednesday at 8:00 P.M. at various member hospitals, Miami, Fla. GREATER ST. LOUIS SOCIETY OF RADIOLOGISTS

Secretary-Treasurer, Dr. Roland P. Ernst, 3720 Washington Ave., St. Louis, Mo. 63108.

HAWAH RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Virgil R. Jobe, Jr., 888 South King St., Honolulu, Hawaii 96813. Meets third Monday of each month at 7:30 P.M.

HEALTH PHYSICS SOCIETY

Secretary, John H. Pingel, Argonne National Laboratory,

9700 S. Cass Ave., Argonne, Ill. 60439. Annual Meeting: Waldorf Astoria Hotel, New York City, July 11-15, 1971.

HOUSTON RADIOLOGICAL SOCIETY

Secretary, Dr. Kenneth M. Jensen, 1615 St. Joseph Prof. Bldg., Houston, Texas 77002. Meets fourth Monday of each month, except June, July, August and December, at 6500 P.M., at 103 Jesse H. Jones Library Building, Texas Medical Center, Houston, Tex. 77025

IDAHO STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary, Dr. Hugh P. Smith, Jr., 130 E. Bannock, Boise, Id. 83702. Meets in the spring and fall.

ILLINOIS RADIOLOGICAL SOCIETY, INC., CHAPTER OF ACR.

Secretary, Dr. Jack L. Melamed, 1230 Sunset Rd. Winnetka, Ill. 60093. Meets in the spring and fall. Indiana Roentgen Society, Inc., Chapter of ACR Secretary, Dr. Dale B. Parshall, Elkhart General Hospital, P.O. Box 1329, Elkhart, Ind. 46514.

IOWA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. John Huston Jr., 1948 First Ave. N.E., Cedar Rapids, Iowa 52402. Luncheon and business meeting during annual session of Iowa State business meeting during annual session of Iowa State Medical Society. The scientific section is held in the

KANSAS RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Wm. R. Allen, 155 S. 18th St. Kansas City, Kan. 66102. Meets in spring with State Medical Society and in winter on call.

KENTUCKY CHAPTER OF ACR

Secretary-Treasurer, Dr. Joan R. Hale, 402 Heyburn Bldg. Louisville, Ky. 40202. Meets in April and September.

KINGS COUNTY RADIOLOGICAL SOCIETY

Secretary, Dr. Sidney Hendler, 1880 Ocean Ave., Brooklyn 30, N.Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Knoxville RadioLogical Society

Secretary, Dr. Clifford L. Walton, Blount Professional
Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

LONG ISLAND RADIOLOGICAL SOCIETY Secretary, Dr. Harold L. Atkins, 1200 Stewart Ave., Garden City, N. Y. 11533. Meets monthly. Los Angeles Radiological Society

Secretary, Dr. Harry T. Vanley, St. Mary's Long Beach Hospital, Long Beach, Calif. 90083. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles, Calif. Annual Midwinter Conference: Jan 30-31, 1971.

LOUISIANA-TEXAS GULF COAST RADIOLOGICAL SOCIETY

Secretary Transport De Edward A Sheldon Los Doctors

Secretary-Treasurer, Dr. Edward A. Sheldon, 109 Doctors Bldg., Beaumont, Tex. 77701

MAINE RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Richard W. Taylor, Radiology Department, St. Mary's General Hospital, Lewiston, Maine 04240. Meets in June, September, December and April. MARYLAND RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary, Dr. Nathan Stofberg, 4519 Hawksbury Rd.,

Pikesville, Md. 21208.

MASSACHUSETTS RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Norman L. Siadowsky, The Faulkner Hosp., 1153 Centre St., Jamaica Plain, Mass. 02130

MEMPHIS ROENTGEN SOCIETY Secretary-Treasurer, Dr. Webster Riggs, Jr., The University of Tennessee College of Medicine, Department of Radiology, Walter F. Chandler Bldg., 865 Jefferson Ave., Memphis, Tenn. 38103. Meets first Monday of each month at John Gaston Hospital.

MIAMI VALLEY RADIOLOGICAL SOCIETY

Sceretary, Dr. Darwood B. Hance, Reid Memorial Hospital, Richmond, Ind. Meets third Thursday of fall, winter and spring months at 7:30 P.M. at Miami Valley Hospital, Dayton, Ohio.
MICHIGAN RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary, Dr. David P. Corbett, Harper Hospital, De-

troit, Mich. 48201. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

MID-HUDSON RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Herbert S. Berlin, Hopewell Junction, N. Y. Meets 7:  $\infty$  P.M., first Wednesday of each month, September to May.

MILWAUKEE ROENTGEN RAY SOCIETY

Secretary-Treasurer Dr. James E. Bell, 8700 W. Wisconsin Ave., Milwaukee, Wis. 53213. Meets monthly on fourth Monday, October through May, at University Club.

MINNESOTA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Warren L. Kump, 4243 Glenwood Ave., Minneapolis, Minn. 55422. Meets twice annually, fall and winter.

MISSISSIPPI STATE RADIOLOGICAL SOCIETY, CHAPTER OF

Secretary-Treasurer, Dr. Ottis G. Ball, 5356 Balmoral Drive, Jackson, Miss. 39211. Meets third Thursday of each month at the Heidelberg Hotel, Jackson, at 6:00 P.M.

MISSOURI RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Arthur A. Porporis, 100 N. Euclid Ave., St. Louis, Mo. 63108.

MONTANA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Jon A. Anderson, Doctor's Building, 1231 N. 29th Street, Billings, Mont. 59101.

NEBRASKA CHAPTER OF ACR

Secretary-Treasurer, Dr. Gordon F. Johnson, 4239 Farnam, Omaha, Neb. 68131. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

NEVADA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Harris W. Knudson, 2020 W. Charleston Blvd., Las Vegas, Nev. 89102.

New England Robentgen Ray Society
Secretary, Dr. Stefan C. Schatzki, 1180 Beacon St.,
Brookline Mass. 02146. Meets third Friday of each month, October through April, excluding December, at The Longwood Towers, 20 Chapel Street, Brookline, Mass., at 4:30 P.M.

NEW HAMPSHIRE ROENTGEN RAY SOCIETY, CHAPTER OF

Secretary, George Farmlett, 33 Round Bay Rd., Keene, N. H. 03:46. Meets four to six times yearly.

New Mexico Society of Radiologists Chapter of ACR Secretary, Dr. Donald A. Wolfel, Albuquerque, New Mexico. Four meetings annually, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

NEW YORK ROENTGEN SOCIETY Secretary-Treasurer, Dr. Samuel H. Madell, t. E. 82nd St., New York, N. Y. 10028. Meets monthly on third Monday at the New York Academy of Medicine at 4:30 P.M. Annual Spring Conference: Waldorf Astoria Hotel, New York, April 29-May 1, 1971. Further information may be obtained from Dr. Albert A. Dunn, Roosevelt Hosp.,

New York, N. Y. 10019. NEW YORK STATE CHAPTER OF ACR

Secretary-Treasurer, Dr. John J. Magovern, 520 Frank-lin Ave., Garden City, N. Y. 11530.

NORTH CAROLINA CHAPTER OF ACR.

Secretary-Treasurer, Dr. James F. Martin, 300 S. Hawthorne Road, Winston-Salem, N. C. 27103.

NORTH DAKOTA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Marshall Landa, 1702 13th St., So., Fargo, N. D. 58102. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

NORTH FLORIDA RADIOLOGICAL SOCIETY
Secretary, Dr. John W. Morris, III., Department of
Radiology, Halifax District Hospital, Daytona Beach,
Fla. 32015. Meets quarterly in March, June, September and December.

NORTHEASTERN NEW YORK RADIOLOGICAL SOCIETY Secretary, Dr. Barbara Chick, Glens Falls Hospital, Glens Falls, N.Y. 12801. Meets in Albany area on third Wednesday of October, November, March, April, and

NORTHERN CALIFORNIA RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Kevin Ryan, Woodland Medical group, Woodland, Calif. 95695. Meets fourth Monday of Sept., Nov., Jan., March and May at Aldo's Restaurant in Sacramento.

NORTHWESTERN OHIO RADIOLOGICAL SOCIETY

Secretary, Dr. Vito J. Zupa, Mercy Hospital, Department

of Radiology, Toledo, Ohio.
Ohio State Radiological Society, Chapter of ACR Secretary, Dr. Joseph Hanson, 1544 South Byrne Road, Toledo, Ohio 43614. Oklahoma State Radiological Society, Chapter of

ACR

Secretary, Dr. Richard B. Price, 204 Medical Tower Bldg., Oklahoma City, Okla. 73112. Meets in January, May and October.

ORANGE COUNTY RADIOLOGICAL SOCIETY

Secretary, Dr. Roderick A. Silveira, 100 E. Valencia Mesa Dr., Fullerton, Calif. 92632. Meets on fourth Tuesday of the month, excluding June, July, August, and December, at the Orange County Medical Association Bldg., Orange, Calif.

OREGON STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Gerlad L. Warnock, 11699 N. E. Glisan St., Portland, Ore. 97220. Meets on second Wednesday of month, October through April, at the University Club, Portland, Ore.
ORLEANS PARISH RADIOLOGICAL SOCIETY

Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans, La. 70113. Meets second Tuesday of each

month.

PACIFIC NORTHWEST RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Robert S. Miller, 13753 S.W. Farmington Rd.; Beaverton, Oregon 97005. Meets annually in Portland, Oregon, Seattle, Washington or Victoria or Vancouver, British Columbia, in early May.

PENNSYLVANIA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Theodore A. Tristan, Harrisburg Polyclinic Hosp., Harrisburg, Pa. 17105.

PHILADELPHIA ROENTGEN RAY SOCIETY

Secretary, Dr. C. Jules Rominger, Misericordia Hospital, 54th St. and Cedar Ave., Philadelphia, Pa. 19143. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

PITTSBURGH ROENTGEN SOCIETY

Secretary, Or. Norman Williams, Department of Radio-therapy, Montefiore Hospital, 3409 Fifth Ave., Pitts-burgh, Pa. 15213. Meets second Wednesday of month, October through June, at Park Schenley Restaurant.

RADIATION RESEARCH SOCIETY

Executive Secretary, Richard J. Burk, Jr., 4211 39th St., N.W., Washington, D. C. 20016.
RADIOLOGICAL SOCIETY OF CONNECTICUT, INC., CHAPTER OF ACR

Secretary-Treasurer, Dr. Carl W. Scheer, 335 Cook Ave., Meriden, Conn. 06450. Meetings are held quarterly RADIOLOGICAL SOCIETY OF GREATER CINCINNATI

Secretary Treasurer, Dr. Donald E. Gunderson, 3553 Bayard Dr., Cincinnati, Ohio 45208. Meets first Monday of each month at Cincinnati Academy of Medicine.

RADIOLOGICAL SOCIETY OF GREATER KANSAS CITY Secretary, Dr. Ken C. Davidson, St. Luke's Hospital of Kansas City, Kansas City, Mo. 84111. Meets 5 times a year on given dates.

RADIOLOGICAL SOCIETY OF KANSAS CITY
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

RADIOLOGICAL SOCIETY OF LOUISIANA, CHAPTER OF ACR Secretary, Dr. Ralph B. Bergerson, 154 Brockenbraugh Ct. Metairie, La. 70005. Meets semiannually during Louisiana State Medical Society meeting and 6 months

RADIOLOGICAL SOCIETY OF NEW JERSEY, CHAPTER OF ACR Secretary, Dr. Sidney Ketyer, St. Elizabeth Hosp., 225 Williamson St., Elizabeth, N. J. 07207. Meets in Atlantic

City at time of State Medical Society meeting and in October or November in Newark, N. J.

RADIOLOGICAL SOCIETY OF RHODE ISLAND, CHAPTER OF ACR

Secretary-Treasurer, Dr. John J. O'Brien, 292 Merry-mount Dr., Warwick, R.I. 02888.

RADIOLOGICAL SOCIETY OF SOUTHERN CALIFORNIA

Secretary-Treasurer, Dr. Gladden V. Elliott, 5565 Grossmont Center Dr., Suite 1, La Mesa, Calif. 92041. Meets three times a year, usually October, February and May.

RADIOLOGICAL SOCIETY OF THE STATE OF NEW YORK Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester, N. Y. 14618.

REDWOOD EMPIRE RADIOLOGICAL SOCIETY
Secretary, Dr. Lee F. Titus, 164 W. Napa St., Sonoma. Calif. Meets second Monday every other month.

RICHMOND COUNTY RADIOLOGICAL SOCIETY Secretary, Dr. M. Pinson Neal, Jr., Medical College of Virginia, 1200 E. Broad St., Richmond, Va. 23219. Meets first Thursday of each month at various hospitals.

ROCHESTER ROENTOEN RAY SOCIETY, ROCHESTER, N. Y. Secretary, Dr. Kenneth E. Robinson, Rochester General Hospital, 1425 Portland Ave., Rochester, N. Y. 14621. Quarterly meetings on the call of the President, at the Rochester Academy of Medicine.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Lorenz R. Wurtzebach, 4200 E. Ninth Ave., Denver, Colo. 80220. Annual meeting: Brown Palace Hotel, Denver, Colo.

SAN ANTONIO-CIVILIAN-MILITARY RADIOLOGICAL SOCIETY Secretary, Dr. Lee F. Rogers, Department of Radiotherapy, Bexar County Teaching Hospital, 4502 Medical Drive, San Antonio, Texas. Meets third Wednesday of each month at Fort Sam Houston Officers' Club at 6:30

SAN DIEGO RADIOLOGICAL SOCIETY

President-Secretary, Dr. Q. H. Lehmann, 5565 Grossmont Center Dr. Suite 1, La Mesa, Calif. 92041. Meets first Wednesday of each month at the Town & Country Hotel.

San Francisco Radiological Society
Secretary-Treasurer, Dr. Warren M. Russel, Franklin
Hospital, Castro & Duboce, San Francisco, Calif. 94114. Meets quarterly at various hospitals (contact Secretary).

SANTA CLARA COUNTY RADIOLOGICAL SOCIETY Secretary, Dr. Emory G. West, 285 S. Drive, Mt. View, Calif. 94040. Meets monthly at the Santa Clara County Medical Association Bldg., 700 Empey Way, San Jose, Calif.

SECTION ON RADIOLOGY, CALIFORNIA MEDICAL ASSOCIATION Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

SECTION ON RADIOLOGY, MEDICAL SOCIETY OF THE DIS-TRICT OF COLUMBIA

Secretary-Treasurer, Dr. Louis Wener, Cafritz Memorial Hosp., 1310 Southern Ave., S.E., Washington, D. C. 20032. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Southern Medical Association Secretary, Dr. Phillip W. Voltz, Jr., 120 Medical Professional Bldg., San Antonio, Tex. 78212.

Secretary, Dr. George F. Crawford, St. Elizabeth Hospital, Beaumont, Tex. Meets annually with the Texas Médical Association.

SHREVEPORT RADIOLOGICAL CLUB

Secretary, Dr. W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday at 7:30 P.M., September to May inclusive.

SOCIETY FOR PEDIATRIC RADIOLOGY

Secretary, Dr. John L. Gwinn, Children's Hospital, 4614 Sunset Blvd., Los Angeles 27, Calif. Annual meeting: Sheraton Hotel, Boston, Mass., September 26-27, 1971.

SOCIETY OF NUCLEAR MEDICINE Secretary, Dr. James J. Smith, 140 E. 54th St., New York, N. Y. Administrative Officer, Mrs. Margaret Glos,

211 E. 43rd St., New York, N. Y. 10017. Annual meeting: Los Angeles, Calif., June 26-July 2, 1971. SOUTH BAY RADIOLOGICAL SOCIETY

Secretary, Dr. Emerson C. Curtis, University Dr., Menlo Park, Calif. 94025. Meets second Wednesday of each month.

SOUTH CAROLINA RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

South Dakota Radiological Society, Chapter of ACR Secretary, Dr. Haakon O. Haugan, 716 Quincy St., Rapid City, S. D. 57701. Meets in spring with State Medical

Society and in fall.

SOUTHERN CALIFORNIA RADIATION THERAPY SOCIETY Secretary-Treasurer, Dr. Aaron G. Fingerhut, 1000 W. Carson St., Torrance, Calif. 90502. Meets quarterly. SOUTHERN RADIOLOGICAL CONFERENCE

Secretary-Treasurer, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 7544, Mobile, Ala. 36607. Annual meeting: Grand Hotel, Pointe Clear, Ala. Jan. 29-31, 1971. SOUTHWESTERN RADIOLOGICAL SOCIETY

Secretary, John M. McGuire, 904 Chelsea, El Paso, Tex. Meets last Monday of each month at 6:30 P.M. in the Paso del Norte Hotel.

TENNESSEE RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Lawrence R. Nickell, Maury County Hospital, Columbia, Tenn. 38401. Meets annually at the time and place of the Tennessee State Medical Association meeting.

TEXAS STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Herman C. Schested, 815 Medical Tower, Room 100, 1550 W. Rosedale St., Fort Worth, Tex. 76104. Annual meeting at the Flagship Hotel on Pier, Galveston, Tex.

THE FLEICHNER SOCIETY

Sciences Bldg., University of Toronto, Ontario, Canada. Meets in Williamsburg, Va., March 1971, in conjunction with a course on "Modern Trends in Roentgenology of the Chest," sponsored by the Virginia Commonwealth University, Richmond, Va.

TRI-STATE RADIOLOGICAL SOCIETY

Secretary, Dr. John H. Marchand, Jr., Methodist Hospital, Henderson, Ky. Meets third Wednesday of Oct., Jan., March and May, 8:00 P.M., Elks Club in Evans-ville, Ind.

University of Michigan Department of Roentgen-OLOGY STAFF MEETING Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital, Ann Arbor, Mich.

Upper Peninsula Radiological Society Secretary, Dr. A. Gonty, Menominee, Mich. Meets

quarterly. UTAH STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Leon M. Neal, St. Benedict's Hospital, 3000 Polk Ave., Ogden, Utah 84403. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

VERMONT RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Edward A. Kupic, Mary Fletcher Hosp., Burlington, Vt. 05401.

VIRGINIA CHAPTER OF ACR

Secretary-Treasurer, Dr. James S. Redmond, Suite 7, Medical Center, Lynchburg, Va. 24501.

Washington, D. C., Chapter of ACR Secretary-Treasurer, Dr. Joan Wohlgemuth, 5021 Seminary Rd., Alexandria, Va. 22311.

WASHINGTON STATE RADIOLOGICAL SOCIETY, CHAPTER OF

ACR: Secretary-Treasurer, Dr. Paul S. Paulson, 1001 Broadway Seattle, Washington 98122. Meets quarterly.

WEST VIRGINIA RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary-Treasurer, Dr. J. Dennis Kugel, 510-517 Med. Arts Bldg. Charleston, W. Va. 25301. Meets concurrently with annual meeting of West Virginia State Medical Society; other meetings arranged by program committee. Westchester County Radiological Society

Secretary, Dr. Edgar Palmer, 650 Main St., New Ro-chelle, N. Y. 10801. Meets on third Tuesday of January

and October and on two other dates.

Wisconsin Radiological Society, Chapter of ACR Secretary-Treasurer, Dr. Robert E. Douglas, 1209 S. Commercial St., Neenah, Wis. 54956. Meets twice a year, May and September.

WYOMING RADIOLOGICAL SOCIETY, CHAPTER 07 ACR Secretary, Dr. J. D. Grant, Memorial Hosp., Sheridan, Wyo. Meets in fall with State Medical Society and in

spring on call of President.

# MEXICO, PUERTO RICO AND CENTRAL AMERICA

Asociación Costabricense de Radiología

Secretary, Dr. Jorge Vargas Segura, Apartado 5367, San José, Costa Rica.

ASOCIACIÓN DE RADIÓLOGOS DE CENTRO AMERICA Y PANAMÁ. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.

Secretary-General, Dr. Roberto Calderón, Calle Central

Oeste No. 218, Managua, Nicaragua, Central America. Meets annually in a rotating manner in the six countries.

Asociación Pubrtorriqueña de Radiología Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional

Bldg., Santurce, Puerto Rico.

Sociedad de Radiología de El Salvador Secretary, Dr. Julio Astacio, 5a Av. Nte. No. 434, San Salvador, Rep. El Salvador.

Sociedad de Radiología de Guatemala

Secretary, Dr. Carlos E. Escobar, 92. Calle A 0-05, Zona 1, Guatemala.

SOCIEDAD MEXICANA DE RADIOLOGÍA, A.C.

Coahuila No. 35, México 7, D.F. Secretary-General, Dr. Bernardo Serviansky. Meets first

Monday of each month. Sociedad Radiológica Panameña

Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panama, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting.

Sociedad Radiológica de Puerto Rico Secretary, Dr. Heriberto Pagán Sáez, Apt. 9387, Santurce, Puerto Rico. Meets second Thursday of each month at 8:∞ P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

### BRITISH COMMONWEALTH OF NATIONS

Association of Radiologists of the Province of Que-

Secretary, Dr. Pierre Archambault, Hopital Charle Le Moyne, 121 Boul. Taschereau, Greenfield Park, P.Q., Canada. Meets four times a year.

BRITISH INSTITUTE OF RADIOLOGY

Honorary Secretary, Dr. G. H. du Boulay, 32 Welbeck St., London, W. I, England. Meets monthly from October until May.

CANADIAN ASSOCIATION OF PHYSICISTS, DIVISION OF MEDICAL AND BIOLOGICAL PHYSICS.

Honorary Secretary Treasurer, Dr. R. G. Baker, Ontario Cancer Foundation, Ottawa Civic Clinic, 1053 Carling Ave., Ottawa 3, Ont., Canada. Annual Congress, to be announced.

Edmonton and District Radiological Society Secretary, Dr. L. A. Koller, Suite 360, Professional Bldg., 10830 Jasper Ave., Edmonton 15, Alberta, Canada Meets third Thursday of each month October to May, except December, at various Edmonton Hospitals.

FACULTY OF RADIOLOGISTS Honorary Secretary, Robert Morrison, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting, Oxford, England, July 2-3, 1971.

FACULTY OF RADIOLOGISTS, ROYAL COLLEGE OF SURGEONS

in Ireland

Registrar, Dr. H. O'Flanagan, F.R.C.P.I., D.P.H., 123

St. Stephens Green, Dublin 2, Ireland.
Section of Radiology of the Royal Society of Medi-CINE (CONFINED TO MEDICAL MEMBERS)

Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, I Wimpole St., London, W. I, England.

CANADIAN ASSOCIATION OF RADIOLOGISTS

Honorary Secretary, Dr. F. Robert MacDonald, Associate Honorary Secretary, Dr. Champlain Charest, 1555 Summerhill Ave., Montreal 25, Que., Canada. Annual meeting: Palliser Hotel, Calgary, Alberta, March 15–19,

MONTREAL RADIOLOGICAL STUDY CLUB

Secretary, Dr. W. Paul Butt, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

SECTION OF RADIOLOGY, CANADIAN MEDICAL ASSOCIATION Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Societé Canadienne-Française de Radiologie
Secretary General, Dr. Guy Duckett, 1385 est, rue Jean
Talon, Montréal, P.Q., Canada. Meets every third Tuesday from October to April.

Toronto Radiological Society

Secretary, Dr. George Wortzman, Toronto General Hosp., Toronto 12, Ont., Canada. Meets second Monday of each month, September, through May.

College of Radiologists of Australasia Honorary Secretary, Dr. T. P. Loneragan, 147 Macquarie St., Sydney, N.S.W., Australia.

### SOUTH AMERICA

Asociación Argentina de Radiología

Secretary, Dr. Lidio G. Mosca, Avda. Fral. Paz 151, Córdoba, Argentina. Meetings held monthly.

ATENEO DE RADIOLOGIA

Secretary, Dr. Víctor A. Añaños, Instituto de Radiologia, Urqiza 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 P.M. in the Hospital Nacional de Centenario, Santa Fe 1300, Rosario.

Colégio Brasileiro de Radiologia Secretary-General, Dr. Miguel Mario, Céntola, Caixa Postal 5984, São Paulo, Brazil.

Sociedad Argentina de Radiología

Secretary-General, Dr. Juan R. Heilbuth Pacheco, Santa Fe 1171, Buenos Aires. Meets first Wednesday evening, April through December.

SOCIEDAD BOLIVIANA DE RADIOLOGÍA

Secretary, Dr. Javier Prada Mendez, Casilla 1182, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia

Secretary, Dr. Armando Rocha Amoédo, Cxa Postal 1532, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

SOCIEDADE BRASILEIRA DE RADIOTERAPIA

Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigaderio Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología

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Secretariat, c/o Holland Organizing Centre, 16 Lange Voorhout, The Hague, The Netherlands. Congress Meeting: Amsterdam, The Netherlands, June 14-18,

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Société Royale Belge de Radiologie

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Société Européenne de Radiologie Pédiatrique President, Dr. George Thomsen, Rigshospitalet (University Hospital), Blegdamsvej 9, DK 2100 Copenhagen, Denmark. Meets in Elseneur, Denmark, May 12-15, 1971.

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South African International Radiological Congress Director, Dr. Paul Sneider, P.O. Box 4878, Johannesburg,

South Africa.



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# ROENTGEN DIAGNOSIS

### HEAD

Touya, E., Touya (h), J. J., Bekerman, C., Otegui, I., Crotti de De Boni, I., Neumark, R., and Navarro, A. Valor de la centellografia encefalica en el estudio de los tumores de la hipofisis. (Value of cerebral centregraphy in the study of pituitary tumors.) Rev. interamer. radiol., 1970, 5, 16–23. (From: Centro de Medicina Nuclear, Clinica Médica Profesor Manlio Ferrari y de la Cátedra de Clínica Endocrinológica Profesor Alfredo Navarro, Facultad de Medicina, Montevideo, Uruguay.)

Radioactive indium was used to study tumors of the sella turcica and parasellar region.

Proved cases of chromophobe and eosinophilic adenoma, craniopharyngioma and tumors of the optic nerve were demonstrated.

The scan constitutes a valuable adjunct to the study of these tumors.—Charles M. Nice, Jr., M.D., Ph.D.

Bannister, Roger. The place of isotope encephalography by the lumbar route in neurological diagnosis. *Proc. Roy. Soc.*, *Med.* Sept., 1970, 63, 921–925. (From: National Hospital, Queen Square, London WCI, England.)

Injection of  $100 \mu c$  of  $1^{131}$  labelled serum albumin into the lumbar subarachnoid space, and evaluation of its fate in the cisterns over a period of 2 hours to 5 days has been the subject of many recent papers. If the isotope goes into the ventricular system, but not over the surface of the brain as in the normal patient, then a diagnosis of dementia due to communicating hydrocephalus (the so-called low pressure hydrocephalus) can be made. Some of the patients with this variety of hydrocephalus benefit from ventriculo-atrial shunting.

Three groups of patients with this type of hydrocephalus were classified by the author.

In the first group of undisputed communicating hydrocephalus, the isotope enters the ventricular system and remains there for several days, never appearing in the cortical subarachnoid region. The pneumoencephalogram shows ventricular enlargement, but no air over the surface of the brain. Usually a history of head injury, meningitis or subarachnoid hemorrhage is found.

In the second group, the isotope enters the ventricle but leaves it within 48 hours and there is some cortical subarachnoid activity. No air gets over the surface of the brain during pneumoencephalography showing that fluid is more successful than air at penetrating defective cortical subarachnoid spaces.

Shunting results have benefited only a few patients in this group.

The third group represents pure cerebral atrophy with the isotope normally going to the cortical sub-arachnoid spaces and not entering the ventricle. The pneumoencephalogram indicates dilated sulci and large ventricles. Shunting does not affect these cases.

The author concludes that the isotope study could be used in coordination with pneumoencephalography, but that it is more reliable and often safer for the patient than the air study.—Harvey I. Wilner, M.D.

DU BOULAY, G., and McALISTER, JOAN. The choice between carotid angiography and brain-scanning in the investigation of tumour suspects. *Proc. Roy. Soc. Med.*, Sept., 1970, 63, 926–930. (From: St. Bartholomew's Hospital, London ECI, England.)

The authors reviewed the cases of about 400 St. Bartholomew's Hospital patients with tumors proven by operation or autopsy. Also, records of all patients who had technetium 99m brain scans at the Hospital up to the middle of 1967 were re-examined. Except for multiple metastases and some "unusual" tumors, such as a corpus callosum glioma, angiography was felt to offer much more information about the type of tumor than did the scan. Posterior fossa tumors were difficult to diagnose by scanning methods.

Different regimes of investigation were proposed in 4 separate groups of patients.

The first group includes patients with signs of a malignant tumor but with no known primary lesion. Angiography should be performed initially; and only if any doubt exists, should a brain scanning be done.

The second group includes patients with plain film roentgenographic changes of a meningioma, and here again angiography should suffice.

If a known primary tumor site other than the brain exists, the scan may be all that is required.

The fourth group of patients includes those with symptoms such as epilepsy of late onset without other evidence of tumor. Since the likelihood of finding a tumor is extremely small, the scanning, being a simpler procedure, is indicated; and only if positive, should the arteriogram be obtained.

The authors fail to emphasize that the fourth group of patients may have arteriovenous malformations, infarcts, or diffuse tumors which cause seizures and may not demonstrate an abnormal scan.—Harvey I. Wilner, M.D.

WILLIAMS, J. P., PRIBRAM, H. F. W., LYNDE, R. H., and SHARPE, A. R. Isotope cisternography in the evaluation of patients with subarachnoid hemorrhage. J. Nuclear Med., Oct., 1970, 11, 592-596. (From: Medical College of Virginia and Virginia Commonwealth University, Richmond, Va., and University of California, Irvine, Calif.)

It has long been known that meningeal thickening may follow subarachnoid hemorrhage, and that communicating hydrocephalus may result.

The authors undertook to study patients who had persistently xanthochromic spinal fluid or bloody spinal fluid with a bleeding lesion confirmed angiographically and at surgery. Cisternography was done with doses of 100  $\mu$ c high specific activity I<sup>181</sup>HSA and a Pho/Gamma III scintillation camera. Anterior and left lateral views of the head were obtained at 2, 4 and 24 hours.

Of 21 patients, 10 showed evidence of communicating hydrocephalus with tracer entering the lateral ventricles. Of these, 8 have subsequently had atrioventricular shunts, with clinical improvement.

Twelve of the patients in this series bled from known aneurysms, and of these 6 developed communicating hydrocephalus. Of 3 patients who had subdural hematomas from subarachnoid bleeding, 2 developed hydrocephalus.

The authors present good evidence to show that isotope cisternography is an important aspect of the follow-up of patients who have had subarachnoid bleeding.—Frederick J. Bonte, M.D.

HEKSTER, R. E. M., and NORDEN, A. A. J. CH. Non-traumatic atlanto-axial displacement after tonsillectomy: a case report. *Radiol. clin. et biol.*, 1970, 39, 357–365. (From: Department of Radiology, University Hospital, Leiden, The Netherlands.)

The patient, an 18 year old girl, complained of severe upper cervical pain following a tonsillectomy. Five weeks after the operation, roentgenograms were obtained and atlanto-axial dislocation diagnosed. Trauma, rheumatoid arthritis and ankylosing spondylitis were ruled out.

The literature pertaining to nontraumatic dislocation of this area is reviewed quite well, particularly the articles relating to tonsillectomy and nontraumatic dislocation associated with cranio-cervical inflammatory processes.

A treatment plan is outlined which consists of skeletal traction of several weeks to obtain stability, followed by a collar or plaster cast support for up to 6 months.—Everett H. Johnston, M.D.

# Neck and Chest

FISCHER, R., BECKER, H. D., JOIST, J. H., and TISMER, R. Pneumocystis carinii pneumonia in adults. *German Med. Monthly*, April, 1970, 15, 177–185. (Address: Privatdozent Dr. R. Fischer, Pathologisches Institut der Universität, Joseph-Stelzmann-Strasse 9, 5 Köln, Germany.)

Only 6 adult cases of pneumocystis carinii pneumonia were reported prior to 1956. Since then the number has steadily increased. These adult cases

have usually been reported in patients with diseases of the lymphoreticular or hematopoietic system on prolonged steroids, cytotoxic agents, and antibiotics. Still the incidence of massive pneumonia remains low in adults.

The authors report on 3 proven adult cases and on negative necropsy material in 120 other cases with diseases of the lymphoreticular or hematopoietic systems. The 3 with pneumocystis pneumonia had been given extensive, prolonged cytotoxic chemotherapy or steroids. The increased use of these drugs plays an important part in the recent increase in cases of adult pneumocystis pneumonia; primary pneumocystis pneumonia in adults without immunosuppressive therapy remains very rare.

The authors believe that the increased use of these drugs is not solely the cause for the increased number of cases. They think that transmission of the agent by carriers with latent infections also plays a role; the 3 reported cases all occurred within a 3 week period of the 5 years studied.

The clinical signs and symptoms consist of an insidious onset with little or no fever, dyspnea and a dry cough. Tachypnea and cyanosis occur with massive progression and infection. Only minimal physical findings of rales are present.

The roentgenologic findings are initially patchy or linear infiltrates in the hilar regions which progress to become denser and more confluent. Upper lobe or apical infiltration and increasing respiratory insufficiency bodes an unfavorable prognosis. Focal infiltrates of a softer nature are a rarer finding. The pleurae are rarely affected and hilar lymphadenopathy and cavities are not observed. The mediastinal emphysema or pneumothorax seen in children is very rare in adults. The roentgenologic findings cannot be considered pathognomonic.

The diagnosis is usually firmly established in the patient with an underlying disease of the lymphoreticular or hematopoietic system on immunosuppressive drugs who presents with the triad of respiratory failure, extensive roentgenologic evidence of pulmonary insufficiency and few physical findings.

Conclusive evidence is the pathologic finding of foamy vacuolar material in the alveolar lumina and identification of the micro-organism from percutaneous lung biopsies; these biopsies are required because unlike children the tracheobronchial smears of adults rarely demonstrate the micro-organism.—

Phillip Godsey, M.D.

BANASZAK, EDWARD F., THIEDE, WALTER H., and FINK, JORDAN N. Hypersensitivity pneumonitis due to contamination of an air conditioner. New England J. Med., Aug., 1970, 283, 271-276. (From: Department of Pulmonary Physiology, St. Luke's Hospital, the Allergy Section, Department of Medicine, Marquette School of Medicine, and the

Research Service, Wood Veterans Administration Center, Milwaukee, Wis.)

The authors discovered the insidious contamination of an air conditioning system by a thermophilic *Actinomycete*.

The patients developed a hypersensitive pneumonitis. Their symptoms, pulmonary function and blood studies reflected their disease.

Roentgenographically a diffuse nodular infiltration of the lungs was a characteristic of the disease.

There was eventual clearing of the infiltration after several months of treatment with steroids and avoidance of exposure to the fungus.—F. Bennett Giles, M.D.

REMOLAR, JORGE M., GOLDEMBERG, BERNARDO, GOLDEMBERG, DORA S. DE, and GROIS, ENRIQUE. Neumonía atípica primaria: su concepto actual. (Primary atypical pneumonia: current concept.) Rev. Argentina radiol., April, 1970, 33, 33-43. (From: Servicio de Clinica Médica del Policlinico Prof. Dr. Gregorio Aráoz Alfaro de Lanús, Buenos Aires, Argentina.)

Included in primary atypical pneumonia are those more or less acute pneumopathies which differ from the classical clinical, laboratory, and roentgenologic picture produced by the *Pneumococcus*. This group includes virus infections, *Mycoplasma* and *Rickettsia* infections.

The present authors also include unusual clinical pictures produced by the *Tubercle* bacillus, *Pneumococcus*, *Influenza* bacillus, *Staphylococcus*, *Histoplasma*, *Blastomyces*, *Coccidioides* and *Pneumocystis carinii*.

In the early stages of atypical pneumonia the roentgenographic changes are more evident than the physical findings. Quite often there is a perihilar infiltration which may later spread into the periphery. Pleural effusion is usually minimal or late in appearing. The roentgen changes may lag behind the appearance of clinical symptoms and may persist after the disappearance of clinical symptoms.

Primary atypical pneumonia should not be a diagnosis of exclusion. Active attempts should be made to perform proper laboratory studies which will lead to more specific diagnosis.—Charles M. Nice, Jr., M.D., Ph.D.

Fine, Norman L., Smith, Lawrence R., and Sheedy, Patrick F. Frequency of pleural effusions in mycoplasma and viral pneumonias. *New England J. Med.*, Oct., 1970, 283, 790–793. (Address: Dr. Fine, Section of Pulmonary Diseases, University of Arizona College of Medicine, Tucson, Ariz. 85721.)

The rarity of pleural effusions has been emphasized in the literature dealing with the roentgenographic

features of mycoplasma and viral pneumonias. It had been previously stated that pleural effusion is so rare in those entities as to suggest an alternative diagnosis. For this reason a prospective study was undertaken at an Air Force Base in Alabama.

Fifty-nine patients with nonbacterial pneumonia satisfied serologic criteria for association with mycoplasma, viral, or cold agglutinin-positive pneumonia. Twelve of these patients were found to have radiologic evidence of pleural effusion, but in 4 its identification required lateral decubitus projection. Those patients with effusions had further work-up to exclude tuberculosis, collagen disease, pulmonary embolus, and mononucleosis.

The authors conclude that pleural effusions occur in a significant percentage of these pneumonias, and that the possibility of a mycoplasma etiology should not be dismissed because of the effusion.—Rosalind H. Troupin, M.D.

Nadel, J. A., Wolfe, W. G., Graf, P. D., Youker, J. E., Zamel, N., Austin, H. J. M., Hinchcliffe, W. A., Greenspan, R. H., and Wright, R. R. Powdered tantalum: a new contrast medium for roentgenographic examination of human airways. *New England J. Med.*, Aug., 1970, 283, 281–286. (From: Cardiovascular Research Institute, Department of Medicine and Department of Radiology, University of California San Francisco, San Francisco, Calif.)

Usual contrast materials used for bronchography have the disadvantage of not being very radiopaque, so that a large volume needs to be introduced into the airways. This alters pulmonary function and does not provide detail of the mucosa.

The authors utilized powdered tantalum in 26 patients with serious lung disease and in whom surgical removal of a part of a lung was anticipated. Selective catheterization was performed and powdered tantalum insufflated. Powdered, gas-sterilized tantalum was utilized.

The airflow was 12 l./sec. from a compressed air tank, into the atmosphere via a side hole in a T-tube or, when the side hole was occluded, into an atomizer, which was grounded and contained 20 gm. of tantalum.

Fine mucosal detail was obtained. The small volume of tantalum used in the segmental studies did not significantly alter pulmonary function. The mean change in airway resistance was 11.6 per cent. The tantalum was cleared in 4 days in 9 patients in whom it was limited to airways 2 mm. or greater in diameter. It was cleared in 7 days in 17 patients where it had been in airways less than 2 mm. in diameter.

Microscopic studies of lung tissue were performed in 14 patients 1 to 93 days following insufflation. In 8, microscopic sections showed no tantalum remaining. Tantalum was present in airways larger than 1 mm. in diameter in 2 patients.

The authors' study shows that bronchograms produced by insufflating powdered tantalum segmentally provide important diagnostic information in patients with serious lung diseases.—Raymond Gize, M.D.

Essinger, A., Hessler, C., Willa, C., Favez, G., and Nour, T. Intégration de l'angiographie pulmonaire dans l'exploration respiratoire. (Integration of pulmonary angiography into the respiratory exploration.) Radiol. clin. et biol., 1970, 39, 192–213. (Address: A. Essinger, Institut universitaire de radiologie médicale, CH-1011, Lausanne, Switzerland.)

Clear demonstration of vascular morphology by pulmonary angiography has made of this procedure a fundamental investigative method in pneumonology. This is based upon the close relationship between pulmonary circulation and oxygenation of blood.

This report relied upon 144 cases of pulmonary angiography (exclusive of cardiac exploration patients). The authors used the Seldinger technique in catheterizing through the femoral veins. For each case, the pressure within the pulmonary artery and the right ventricle and atrium was measured. The contrast medium was injected into the pulmonary arterial trunk immediately above the valvular plane. Thus pulmonary arteries and their branches were satisfactorily visualized and circulation time evaluated by comparing the right and left sides. In certain cases, based upon the clinical findings, selective angiography with injection into a lobar or even a segmental branch of a pulmonary artery was performed, enabling visualization of much smaller vessels. In such a case, both the arterial and venous phases of circulation were serially roentgenographed.

The angiographic findings can be divided into 3 groups. The first group is comprised of bilateral generalized pathologic changes. Roentgenologic interpretation of such cases is difficult because of poor visualization of peripheral vessels. However, in advanced emphysema and pulmonary hypertension, there is generally an important dilatation of the pulmonary arteries and trunk and marked alterations of the smaller vessels. The second group includes unilateral pathology when it is easy to compare the abnormal vascular pattern with the normal side. Thus in McLeod's syndrome, one notes a spectacular amputation of the pulmonary artery on the pathologic side. The third group is composed of focal pathology. Pulmonary angiography is often very helpful as to differential diagnosis. However, at times, interpretation of denser and more extensive focal lesions by means of angiography could become difficult because of the minuteness of the vessels.

Angiographic modifications can be grouped into 3

types: (1) displacement of pulmonary vessels in the arterial phase (for example, in case of large emphysematous bullae); (2) vascular rarefaction at the site of pathology (normal inflammation); (3) modifications in the morphology of the pulmonary arteries such as abrupt amputation of an artery or bayonet type of deformity as to segmental branches or neoplastic invasion of arterial walls (truncated appearance). Chronic inflammatory lesions definitely diminish the vascularity of the region because of fibrotic changes.

A few of the typical cases are reported in detail, accompanied by fine pulmonary angiographic reproductions.— Firair N. Sarian, M.D.

GOGGIN, M. J., THOMPSON, F. D., and JACKSON, J. W. Deceleration trauma to the heart and great vessels after road-traffic accidents. *Brit. M. J.*, June 27, 1970, 2, 767–769. (Address: M. J. Goggin, M.B., Lecturer in Nephrology, Institute of Urology, London W. C. 2, England.)

Four case histories of young men involved in high speed accidents are described; they were all subjected to sudden deceleration.

Two cases resulted in aneurysms of the descending thoracic aorta just distal to the left subclavian artery. A third case resulted in a splitting of the posterior cusp of the mitral valve with detached chordae. The fourth case developed a ventricular septal defect. All 4 cases were proven at operation.

The authors discuss the literature relevant to the deceleration injuries of the heart and great vessels. In aortic injuries, early angiography, serial chest roentgenography and electrocardiography are emphasized. Upper mediastinal widening is a suspicious finding indicating possible aortic tear. Traumatic mitral incompetence and ventricular septal defects are rare injuries.

Early diagnosis is emphasized since surgical correction can often be performed.—Robert Dormire, M.D.

# ABDOMEN

Valer, Amador Holgado, and Villanueva, Fernando Esparza. El reflujo gastroesofagico en el estudio de la pirosis. (Gastroesophageal reflux in the study of pyrosis.) Rev. interamer. radiol., 1970, 5, 37–46. (From: Universidad Peruana Cayetano Heredia y Departamento de Radiología del Hospital Militar Central, Lima, Perù.)

After the stomach is well filled with barium, the patient is placed in the left lateral depubitus position, following which he is rotated into the right posterior oblique position.

The patient is then instructed to drink cold water through a straw under fluoroscopic control. It was found that there was a very high correlation of a positive siphonage test with the symptoms of pyrosis.

Reflux has been demonstrated in relatively normal infants, in the late months of pregnancy, and in patients with hiatal hernia.

Some patients without hiatal hernia who have a peptic ulcer or other upper gastrointestinal complaints also show reflux and reflux may be demonstrated after cardiomyotomy for achalasia.

Patients with phrenic nerve paralysis usually do not demonstrate reflux.—Charles M. Nice, Jr., M.D., Ph.D.

McAdam, W. A. F., and Goligher, J. C. The occurrence of desmoids in patients with familial polyposis coli. *Brit. J. Surg.*, Aug., 1970, 57, 618–631. (From: University Department of Surgery, The General Infirmary, Leeds, England.)

Desmoids are a peculiar form of aggressive fibromatosis occurring without encapsulation, usually within the anterior abdominal wall. They never metastasize; however, they generally do recur after incomplete excision. They occur only rarely in the general population but are comparatively common in people with familial polyposis.

Gardner's syndrome is a combination of ectodermal and mesodermal tumors with familial polyposis, and it is now estimated that approximately 10 per cent of individuals with polyposis manifest this syndrome. It is thought possible that desmoid formation is probably just another variant of this syndrome. Four additional cases of desmoid tumor and familial polyposis are reported, bringing to 89 the number of cases in the literature. In half of these, the desmoid either extended to or arose from an intraabdominal location.

Two important practical considerations emerge. Since the appearance of desmoids may antedate the discovery of polyposis by months or years, any patient who is found to have a desmoid should be examined for polyposis coli. Conversely, after surgery for polyposis, no abdominal mass should be regarded as recurrent adenocarcinoma until proven so by adequate biopsy.—Rosalind H. Troupin, M.D.

LAGUNDOYE, S. B., and ITAYEMI, S. O. Tension pneumoperitoneum. *Brit. J. Surg.*, Aug., 1970, 57, 576–580. (From: Departments of Radiology and Surgery, University of Ibadan and University College Hospital, Ibadan, Nigeria.)

Tension pneumoperitoneum is defined by the presence of a valve-like mechanism which allows air to enter the peritoneal cavity from the gut, without it being able to escape in the opposite direction. If the amount of gas is small there may be no constitutional disturbance; if, however, large quantities of

gas are involved, abdominal distention and diaphragmatic elevation may produce discomfort.

The authors review the literature and report 2 new cases from the University College Hospital, Ibadan, Nigeria. One was seen as a complication of abdominal and pelvic tuberculosis, with tuberculous ulcers of the colon detected at autopsy. The other patient developed tension pneumoperitoneum following puerperal sepsis. In neither case was the precise site of perforation detected nor were gas forming organisms grown on culture.—Rosalind H. Troupin, M.D.

# SKELETAL SYSTEM

HOHMANN, D., and GASTEIGER, W. Zur Röntgendiagnostik der Costotransversalgelenke. (Roentgen diagnosis of the costotransverse joints.) Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin, June, 1970, 112, 783-789. (Address: Prof. Dr. D. Hohmann, Orthopädische Universitätsklinik, 852 Erlangen, Rathsbergerstrasse 57, Germany.)

The costotransverse joints usually cannot be recognized on conventional roentgenograms of the chest. Only a lordotic view may demonstrate these joints in the upper part of the thorax. For a specific study, it is recommended that the roentgen tube be tilted 30° degrees toward the head in the anteroposterior projection with the central beam aimed at T6. When a kyphosis is present, the angle must be increased to 35 and 40 degrees. In severe kyphosis, a raising of the pelvis becomes necessary.

Two additional views with a tilted tube aimed at T<sub>4</sub> and T<sub>8</sub> are also recommended. Oblique views with a 20°degree rotation of the patient have proved valuable in the lower thoracic area. Turning of the body to the right will unfold the joints on the left side and vice versa. An additional anteroposterior projection with a caudad tilt of the tube, aimed at T<sub>4</sub>, aids in differentiating osteoarthritis of the costotransverse joints from degenerative changes of the ligamentum tuberculi costae.

The costotransverse joints were evaluated in 2,028 patients comprising 987 men and 1,041 women. Osteoarthritis was found in 6.05 per cent (4.39 per cent in men and 7.59 per cent in women). It occurred more often in the lower joints with a frequency of 36.7 per cent at T11 against 0.62 per cent at T1. Patients with a kyphosis presented no increased frequency of osteoarthritis as compared with those having a normal curve. On the other hand, degenerative changes occurred less often proportionately in the scoliotic rib cage.

Arthritic changes associated with rheumatoid spondylitis were observed in 38 patients (1.7 per cent). Again the craniad joints were less involved than the caudad ones as in osteoarthritis. Post-traumatic and postoperative changes and those as-

sociated with anomalies of the rib cage were also noted.—Ernest Kraft, M.D.

DIHLMANN, W., and FERNHOLZ, H. J. Radiological signs of gout. German Med. Monthly, April, 1970, 15, 211-213. (Address: Privatdozent Dr. W. Dihlmann, Abteilung Radiologie der Medizinischen Fakultät der Technischen Hochschule, Göthestrasse 27-29 Aachen, Germany.)

The initial diagnosis of gout is usually not a roentgenologic one. The authors discuss the difficulty of the initial diagnosis clinically; therefore, recognizing early roentgenologic changes in suggesting the diagnosis in many chronic cases is important.

The gouty changes are the result of monosodium urate deposition. Working with the hypothesis of concentration/time ratio of urate precipitation, the authors divided the cases of gout into 3 categories: (1) massive deposition in a short time; (2) more protracted deposition at a low concentration; and (3) a high concentration.

The authors explored the early roentgenographic features in each case suspicious of gout, such as hallux-rigidus arthrosis, or suspicion of bony tophi by punched out areas and also by irregular periarticular osteolysis which often spreads towards the diaphysis. These changes eventually end in characteristic, if not pathognomonic (e.g., the "overhanging bone margin") findings.—William A. Kyle, M.D.

MÜSSBICHLER, HERBERT. Arteriographic findings in necrosis of the head of the femur after medial neck fracture. Acta orthop. scandinav., 1970, 41, 77–90. (From: Department of Diagnostic Roentgenology and Department of Orthopaedic Surgery, University of Umeå, Umeå, Sweden.)

Arteriography was carried out on 21 hips with necrosis of the femoral head as diagnosed roentgenographically based on the usual criteria. In 10 of these cases the contralateral unaffected hip was also examined and the arteriographic appearance compared. Later cases were studied by percutaneous catheter with serial filming at the rate of 1 film per second, for 15 seconds.

The blood supply to the region of the hip is reviewed and diagrammed. The previous literature regarding arteriography of this area is briefly reviewed.

The author found that there were: delayed circulation in the posterior collum branch of the medial circumflex artery; nonfilling of the superior retinacular artery; increased filling of the acetabular and ligamentum teres arteries; and increased vascularization near the fracture site in 14 cases. In the other 7 cases, with complete necrosis of the femoral

head, there was no area of increased vascularization identified.

In the normal contralateral hip the posterior collum branch always filled. Inconstant filling, however, was noted in the other arteries.

The author concludes that there is a significant difference in the angiographic appearance between the normal hip and a hip suffering fracture and necrosis of the femoral head fragment.—Everett H. Johnston, M.D.

FURMAN, ROBERT, NICHOLAS, JOHN J., and JIVOFF, LEO. Elevation of the serum alkaline phosphatase coincident with ectopic-bone formation in paraplegic patients. J. Bone & Joint Surg., Sept., 1970, 52-A, 1131-1137. (Address: Robert Furman, M.D., 22 White Street, Rockland, Maine 04841.)

Ectopic bone formation has been found in a variety of conditions including paraplegia, multiple sclerosis, hemiplegia, and meningioma of the spinal cord.

Microscopically the lesion is composed of mature bone and not soft tissue calcification.

A synonym for the condition is paraosteoarthropathy; in this the bone may be adjacent to the joint capsule but is not within the capsule.

Fifteen paraplegic patients were followed by the Rehabilitation Medical Service of the Upstate New York Medical Center from July 1965 to December 1967 Ectopic bone formation occurred in 7 patients and was accompanied by elevations of the serum alkaline phosphatase. In the 8 patients in whom ectopic bone formation did not occur, there was no significant elevation of the serum alkaline phosphatase.

Serum alkaline phosphatase is an aid to the early diagnosis of ectopic bone formation as well as in following the course of the disease.

Roentgenograms were not made at frequent enough intervals in all patients to allow the precise timing of the onset of the bone formation. The lesion, when demonstrable roentgenographically, was found from 6 to 18 weeks following injury.

Ectopic bone formation developed about large joints and never was demonstrated to have occurred around the ankles, wrists, fingers or toes.—Harvey I. Wilner, M.D.

# BLOOD AND LYMPH SYSTEM

Schmidt, H., and Weber, J. Zum diagnostischen Wert des Angiotomogramms. (Diagnostic value of the angiotomogram.) Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin, June, 1970, 112, 746-753. (Address: Prof. Dr. H. Schmidt, Strahlendiagnostische Abteilung des Allgemeinen Krankenhauses, Hamburg-Altona, 2 Hamburg 50, Allee 164, Germany.)

Angiotomography represents a special procedure with distinct advantages but also with some reservations. As a supplementary method it requires a separate injection of contrast material after completion of conventional angiography. Such additional injection may increase the frequency of complications, especially in cerebral arteriography. Another disadvantage is caused by the blurring of vital structures with the exception of a selected body section. Therefore, only a relatively thin section remains in sharpest focus. Simultaneous exposure technique of different layers with a book cassette cannot always be applied, but with increased experience one can properly aim at selected body layers in most instances.

The advantages of angiotomography include: (1) proper determination of the depth of a lesion; (2) clearing of superimposed densities; and (3) detection of clinically suspected lesions which cannot be demonstrated with the conventional angiogram.

The spleen with its vascular tree can best be demonstrated with angiotomograms. The left gastric artery can be separated from the splenic artery and minute branches of the pancreatic arteries become visible. Angiotomography also represents the best method to separate the left colic from the sigmoid artery. Additional vascular structures which can be exhibited include the testicular, internal pudendal, ureteral, uterine, superior and inferior vesical arteries, also the obturator and gluteal arteries. Furthermore, the depth of branches of the subclavian arteries and of other structures can be determined. Cerebellar lesions and occlusion of the gastroduodenal artery can be clearly demonstrated.

Angiotomography is always indicated when the conventional angiogram fails to confirm clinically suspected lesions.—*Ernest Kraft*, M.D.

Hopf, M. A. La cavographie, méthode complémentaire de la lymphographie: à propos de 201 cas consécutifs. (Cavography, a complementary method to lymphography: concerning 201 consecutive cases.) Radiol. clin. et biol., 1970, 39, 177–179. (Address: Institut de radiologie, Clinique générale, Avenue Eugène Pittard 22bis, CH-1206 Geneva, Switzerland.)

Modern diagnostic methods such as lymphography and cavography have given great impetus to investigation of retroperitoneal spaces.

The author has employed these 2 methods simultaneously in 201 of 254 lymphographic cases since 1967 Thus he was able to discover retroperitoneal pathology in 22 patients in whom lymphography was negative. This represents 11 per cent of the 201 cases. Moreover, in 27 patients, or 30 per cent, cavography gave greater information on the pathologic process already diagnosed by lymphography. In addition, urographic views obtained 10 minutes after injection of a water soluble opaque medium

(injected through the external iliac veins by means of a Seldinger needle) for cavography gave further information on the already diagnosed pathology. Hence, cavography is advisable the day after lymphography (by injection of lipiodol from the dorsum of foot) especially if information obtained through lymphography has been negative, unsatisfactory, or incomplete.—Firair N. Sarian, M.D.

Langhammer, H., Hör, G., and Pabst, H. W. Zur diagnostischen Diskrepanz von abdominaler Lymphknotenszintigraphie und röntgenologischer Lymphographie. (Diagnostic discrepancy of abdominal lymph node scintigraphy and roentgenologic lymphography.) Röntgen Blätter, June, 1970, 23, 261–269. (Address: Dr. med. H. Langhammer, Institut und Poliklinik für Physikalische Therapie und Röntgenologie der Universität München, 8 München 15, Ziemssenstrasse 1, Germany.)

Abdominal lymph node scintigraphy represents a well established procedure. Nevertheless, diagnostic results frequently differ from the lymphographic findings. Three cases are reported to illustrate such divergence

The first patient, a 58 year old man, presented with Brill-Symmers' disease. The lymphogram showed generalized giant cell type lymphadenopathy of inguinal, iliac and paraaortic lymph nodes. The scintigram, however, failed to confirm the lymphadenopathy but showed a normal storage in the iliac and inguinal lymph nodes instead.

The second patient with Hodgkin's disease had a normal lymphogram, while the scintigram suggested lymphadenopathy.

In the third patient, the lymphographic findings also proved normal, while the scintigrams suggested a complete block of the paraaortic lymph nodes.

False-negative scintigrams are considered an exception while false-positive findings can be frequently observed. Small metastatic storage defects as well as lymphadenopathy with pathologic tissue structures cannot be recognized with certainty on the scintigrams. Therefore, supplementary lymphography is always necessary for confirmation of pathologic as well as normal findings.—Ernest Kraft, M.D.

VAUGHAN, B. F., SLAVOTINEK, A. H., and JEPSON, R. P. Edema of the lower limb after vascular operations. Surg., Gynec. & Obst., Aug., 1970, 131, 282–290. (From: Departments of Surgery and Radiology, the Royal Adelaide Hospital, Adelaide, South Australia.)

Edema following successful arterial reconstruction

of a previously ischemic lower limb is commonly the postoperative swelling of the leg.—Reuben Jones, observed. Despite several theories, the mechanism is not fully understood.

In an effort to clarify the situation, lymphangiograms were obtained at varying intervals after vascular operations on 24 volunteer patients. Ten had undergone femoropopliteal bypass procedures; 3 had femorofemoral crossover bypass procedures. Other patients studied had undergone resection of aortic aneurysm, excision of a false aneurysm of the common femoral artery, exploration of a popliteal artery, aortoiliac disobliteration, superficial femoral artery reconstruction after arterial trauma, and 2 patients were studied after a femoral herniorrhaphy and a Smith-Petersen arthroplasty. In all 20 patients, lymphangiographic studies of the greater saphenous system were performed. In 4 other patients, the lesser and deep lymphatic systems were investigated after femoropopliteal bypass procedures.

Marked swelling of the lower limb was observed in 10 of the 20 patients and was most noticeable distal to the knee joint. The edema became apparent within 24 hours after operation and increased once the patient became ambulatory. It subsided slowly during the 3rd and 4th postoperative weeks. In some patients persistent swelling remained up to 6 months.

Operations performed at or to the bifurcation of the common femoral artery resulted in only mild edema. Femoral popliteal bypass procedures almost invariably produced severe edema of the limb. The degree of edema was proportional to the number of lymphatic channels damaged.

The removal of the great saphenous vein produced only moderate swelling in 2 of 3 patients, lymphatic damage being confined to the inguinal lymph node region. No abnormality of lymphatic channels was noted in 2 patients with a Smith-Petersen cup arthroplasty or a femoral hernia repair.

The lymphatic trunks were found to be damaged frequently during the course of femoropopliteal bypass procedures. The commonest sites for interruption were at the medial aspect of the knee and in the mid-thigh region. The average number of patent lymphatics remaining in the superficial lymphatic system after the 10 femoropopliteal bypass procedures was only 1.7 per patient as compared to 9.5 for normal. Lymphangiograms obtained 3 weeks later demonstrated dermal backflow. Note is made of a patient who had undergone a femoropopliteal bypass because of occlusive disease, on whom the incision in the thigh was placed more posteriorly than usual. A lymphangiogram demonstrated patency of almost all lymphatic channels; this patient's edema was negligible. Demonstration of deep lymphatic channels in 4 patients having undergone femoropopliteal bypass showed interruption of these deep channels in the upper thigh.

Several other theories of edema following vascular procedures are discussed.

Lymphedema is a major contributing factor in

M.D.

# RADIATION THERAPY

PAUNIER, J.-P., THÉVENOZ, F., and FAR-HOUMAND, P. La place de la radiothérapie dans le traitement de la polyarthrite rhumatoide. (The place of radiotherapy in the treatment of rheumatoid polyarthritis.) Radiol. clin. et biol., 1970, 39, 294-296. (Address: Dr. J.-P. Paunier, Centre de radiothérapie, Hôpital Cantonal, CH-1211 Geneva 4, Switzerland.)

The authors, based on results of radiotherapy of 31 patients (with 71 sites of irradiation) believe in the secondary importance of such treatment. Radiotherapy was successful in recurrent and painful swelling of hands and wrists, where medical treatment had failed. Synovial effusions which were medically helped but recurred after tapping, were benefitted by radiotherapy. Roentgen treatments alleviated pain in the shoulders (but not in the elbows or the ankle) in cases which were otherwise medically controlled but not responding to common analgesics.

Each site was irradiated using 2 opposing fields, each receiving 75 rads skin dose successively. Thus, the hands and wrists were treated with a total dose of 2× 375 rads at 160 kv. The knees and shoulders received 2×750 rads at 200 kv. The elbows were given 2×600 rads and the ankles 2×450 rads at 200 kv. Of the 71 sites irradiated, 60 sites responded satisfactorily.—Jirair N. Sarian, M.D.

# RADIOISOTOPES

Preston, David F., and Greenlow, Robert H. "Hot spots" in lung scans. J. Nuclear Med., July, 1970, 11, 422-425. (From: University of Kentucky College of Medicine, Lexington, Kv.)

Regions of increased accumulation of radionuclide (hot spots) were found in lung scans of patients in whom there was difficulty performing a satisfactory venipuncture.

The authors performed in vitro studies in which MAA was allowed to remain in contact with blood. They found a decreased clotting time, which suggested that the particles accelerated the clotting process. If a clot was added to a suspension of MAA particles, an increased accumulation of activity was found on the clot.

Why MAA accelerated the clotting process, and accumulates on clots remains unclear. However, to prevent the artifact of "hot spots" on lung scans, blood should not be permitted to clot in the MAA syringe.—H. William Strauss, M.D.

DEYSINE, MAXIMO, ROBINSON, RICHARD G., and WILDER, JOSEPH R. Abscess detection by radioactive chromium labeled autologous white blood cells. Surg., Gynec. & Obst., Aug., 1970, 131, 216–220. (From: Departments of Surgery, Hospital for Joint Diseases and Medical Center, and the Mount Sinai School of Medicine, New York, N. Y.)

To detect septic abscesses in rabbits, autologous white blood cells (WBC) with minimal red blood cell contamination were harvested by paracentesis 15–18 hours after the intraperitoneal administration of saline. After incubation with Cr<sup>51</sup> to label the WBCs, ascorbic acid was added to convert any remaining chromium to the trivalent form to prevent subsequent labelling of red blood cells.

Abscesses were created by the implantation of a barium-feces capsule. The labelled WBCs were injected intravenously 3 hours after the capsule was implanted. Scannings were performed 1 to 24 hours thereafter.

Seventy per cent of the rabbits (14/20) had the lesion detected 1 hour after administration of labelled WBCs. In the others, the lesion was detected 2 to 24 hours after administration. There was no interfering activity in the liver or spleen in any animal. However, the renal excretion of Cr<sup>11</sup> caused bladder activity in all cases. This interfering activity was eliminated by emptying the bladder prior to scanning.

The authors suggest that this type of study should be applicable to humans.—H. William Strauss, M.D.

HARVEY, R. F. Direct comparison of a small gamma camera with a rectilinear scanner for thyroid scintigraphy. *Clin. Radiol.*, July, 1970, 21, 261–265. (From: Institute of Nuclear Medicine, Middlesex Hospital Medical School, London W. 1, England.)

A direct comparison of the efficiency of the gamma camera with that of a conventional rectilinear scanner was made in 61 patients referred for thyroid scanning with a variety of diagnoses.

Scintigrams were made 24 hours after an oral dose of 20  $\mu$ c of I<sup>181</sup>. The scanner was a Mecaserto type MO4 with a 4 inch crystal. The scanning time was 15 to 20 minutes. The gamma camera used was that previously described by Saunders and Loveday (1963) and modified for superimposition of the scan on a photograph of the patient's neck; 3,000 to 5,000 counts were used; and the scanning time was usually 5 minutes.

Scans were obtained by both methods and 2 Polaroid pictures were made of the patient's neck. The scintigrams were superimposed over the Polaroid pictures. A comparison was then made regarding the picture obtained in each case and the relative values of the contribution to the clinical problem.

The quality of the scan obtained with the small camera indicated that good results were obtained in 56 per cent of the patients as compared to 82 per cent obtained with the scanner. However, in terms of information produced in relation to the clinical problem, a satisfactory answer was given in 52 of 61 cases (85 per cent) by the camera and in 58 of 61 (95 per cent) by the scanner.

There was no difference between the camera and the scanner in localization of the thyroid gland, assesment of recurrence of thyroid carcinoma after surgery and in determination of the activity of palpable nodules over 2 cm. in diameter.—Charles W. Cooley, M.D.

TAUXE, W. NEWLON, BROADBENT, JAMES C., and THORSEN, HELEN C. Disappearance of iodoalbumin from pericardial sac in a patient with myxedema. J. Nuclear Med., Sept., 1970, 11, 554-558. (Address: W. Newlon Tauxe, Section of Clinical Pathology, Mayo Clinic, Rochester, Minn. 55901.)

Pericardial effusion secondary to myxedema has been known to persist after the myxedema has been treated. There have been few data published on the actual turnover rates of pericardial fluid.

A case is presented of a 60 year old woman who was myxedematous and who had a pericardial effusion. She was seen in 1966 and was treated with dextrothyroxine (choloxin). There was considerable improvement in her symptoms in 6 months and she was practically euthyroid. The chest roentgenogram showed a marked cardiac enlargement that was unchanged from the previous study. The electrocardiogram showed no change from the previous study.

A cardiac scintiscan was made after the injection of 200  $\mu$ c of iodinated (I<sup>181</sup>) human serum albumin. The scan showed a pericardial effusion. Four days later a pericardiocentesis was done and 200  $\mu$ c of I<sup>181</sup> human serum albumin was injected into the pericardial sac. Serial scans were done for 9 days. The scans were made with a 3 inch Picker Magnascanner. The data were digitized and computer processed. Total count rates were obtained over the pericardium. The net count rates were corrected for decay and plotted against time on semilogarithmic paper. The slope of the curve indicated a disappearance rate of 1.5 per cent per day.

It is not clear from the data whether the slow clearance rate of the labelled albumin had been caused by or was associated with a prior myxedematous state.—Charles W. Cooley, M.D.

GILLESPIE, P. J., EDELSTYN, G. A., and KEYES, W. I. Rectally administered radio-iodide in the detection of hepatic metastases. *Clin. Radiol.*, July, 1970, 21, 266–269. (From:

Northern Ireland Radiotherapy Centre, Purdysburn, Belfast, U.K.)

Ratzkowski (1963), Ernst (1964) and Tukianen (1968) reported a method for the early detection of hepatic metastases, which consisted of the rectal administration of 50  $\mu$ c of NaI<sup>131</sup> and the continuous chart recording of the rise in the count rate over the liver. Normal livers gave a count rate that increased rapidly to a maximum and reached a plateau within 9 minutes. In patients with hepatic metastases the plateau was reached between 14 and 30 minutes.

The authors studied 32 patients over a 2 year period. There were 12 controls and 20 patients with strong evidence of liver metastases. The procedure consisted of injecting 50  $\mu$ c of NaI<sup>17</sup> in 10 ml. of water into the rectum. The test was run until either the uptake pattern became evident or 30 minutes had elapsed. The scintillation counter had a 2 inch crystal and was coupled to a linear chart recorder.

In only a few cases was a plateau reached. Many of the uptake curves on the control patients rose continuously over periods longer than 9 minutes and many with metastatic involvement produced uptake patterns in which the 80 per cent level was attained before 14 minutes had elapsed.

The traces were analyzed regarding the time for the count rate to reach 80 per cent of its final value, the count rate at 2 minutes and 10 minutes expressed as percentage of the final count rate and the mathematical description of the uptake curve which was considered to be a single exponential function. No correlation could be found in the above studies and the clinical status of the patient.—Charles W. Cooley, M.D.

Quaife, Merton A., and Wilson, William J. Detection of cardiac tumor by rectilinear imaging with <sup>181</sup>Cs. J. Nuclear Med., Oct., 1970, 11, 605–607. (From: University of Nebraska Medical Center, Omaha, Neb.)

Primary neoplasms of the heart are exceedingly rare, comprising less than 0.002 per cent of almost 500,000 cases in an autopsy series.

The authors report the case of a patient who was a 17 year old girl with a long history of presumed familial myocardiopathy. Three siblings were reported to have had heart murmurs, and I brother had died following open heart surgery for a ventricular septal defect. On examination the patient had loud, harsh systolic and diastolic murmurs, the latter being interpreted as a pericardial friction rub. A rectilinear heart blood pool scan made with Tc<sup>99</sup>m pertechnetate revealed a diminished level of radioactivity near the cardiac apex. A myocardial scan with Cs181 was then performed and showed a defect in the pattern of cesium uptake, also in the region of the cardiac apex. At surgical exploration a mass measuring 5 cm. in diameter was found to occupy the apex of the left ventricle. So hard in consistency was it, that needle biopsy could not be carried out. Incisional biopsy specimen was reported on frozen section examination to be a fibroma, and the tumor was then successfully excised. The endocardium was found to be intact over the area occupied by the tumor. The patient tolerated the procedure well.

The authors briefly review the literature on myocardial fibromas, of which 30 had been reported prior to this paper. The majority have been found in children with no sex predisposition. Clinical manifestations may include congestive failure or arrhythmia of obscure origin, and sudden death.

The combination of blood pool and myocardial scanning comprises a good diagnostic approach to this rare disease.—Frederick J. Bonte, M.D.

Musso, A. M., Kremenchuzky, S., and Rochna Viola, E. M. Simultaneous study of the absorption of tritiated pteroylglutamic acid and 60 Co-vitamin B<sub>12</sub>. J. Nuclear Med., Oct., 1970, 11, 569-575. (From: Centro de Medicina Nuclear del Hospital Escuela José de San Martín, Buenos Aires, Argentina, Comisión Nacional de Energía Atómica, Argentina, and St. Bartholomew's Hospital Medical College, London, England.)

Impaired intestinal absorption of vitamin B<sub>12</sub> and/or folic (pteroylglutamic) acid is due mainly to disease of the stomach or small bowel. Also, malabsorption of these vitamins may occur following gastrointestinal surgery. Deficiency of either of these substances results in megaloblastic anemia.

Although a number of procedures have existed by which absorption of either vitamin B13 or folic acid could be determined separately, the authors felt that a combined method was more suitable. Accordingly double tracers including 3 H folic acid and Co50 vitamin B12 are simultaneously administered, and are assayed by spectrometric beta counting. Each tracer was administered in a single combined oral dose which contained amounts of each vitamin within the range of their daily physiologic requirement. The test consisted of measuring unabsorbed fecal radioactivity until 2 consecutive specimens contained less than I per cent of each ingested isotope after the peaks of activity had appeared. A liquid scintillation spectrometer was used in radioassay.

The procedure was tested in 2 control subjects, 3 patients with chronic atrophic gastritis and 4 patients with megaloblastic anemia diagnosed by peripheral blood and bone marrow examination.

The results indicated that the combined test gave a quantitative estimate of the absorption of these 2 related compounds at the same point in time, and under defined conditions.

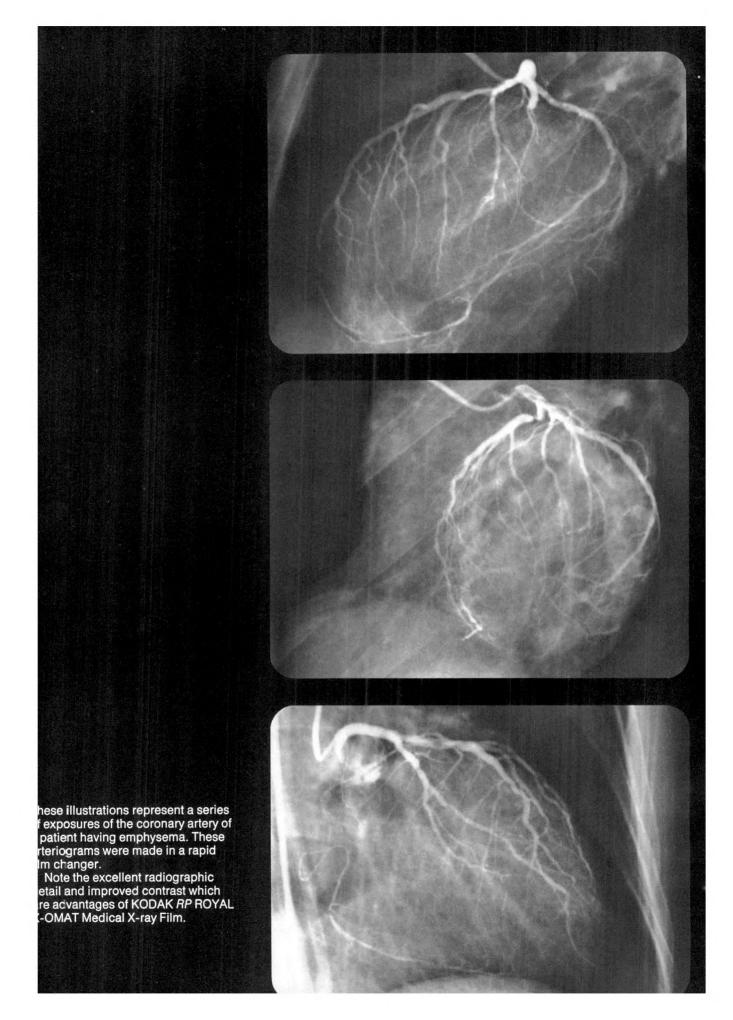
The authors believe that the test will be useful in studying patient response to therapeutic trials.—
Frederick J. Bonte, M.D.

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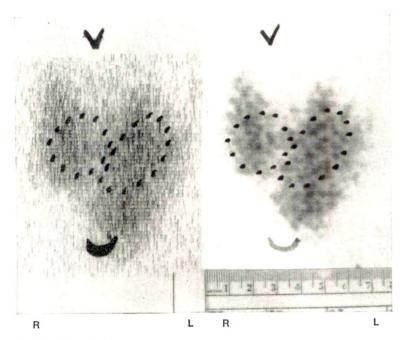
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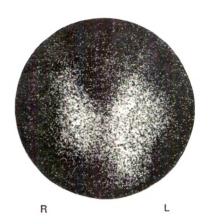
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# TOXIC NODULAR GOITER. RHEUMATIC HEART DISEASE.



RECTILINEAR SCANS.
Isotope: 1311 iodide. Dot scan (left). Photo scan with 61-hole collimator.
0% suppression. Scan time 10 minutes. Broken lines define palpable nodules not evident in scan recordings.



PHO/GAMMA SCINTIPHOTO. Isotope: <sup>131</sup>I iodide. Pho/Gamma equipped with single-pinhole collimator. Total counts 10,000. Total exposure time 3 minutes, 32 seconds. Cold nodule evident in left lobe (see text).



THE PHO/GAMMA SCINTILLATION CAMERA

# Th Thyroid Study

# A Basic Technique for Evaluation of Regional Thyroid Function with the Nuclear-Chicago Pho/Gamma® Scintillation Camera

Scintiphotography, using <sup>131</sup>I iodide and the Pho/Gamma Scintillation Camera, serves as both a primary diagnostic method and as a supplement to rectilinear scanning in the evaluation of thyroid function.

**SETTING-UP.** The patient is positioned with his thyroid at the appropriate distance (usually about 3 inches) from the aperture of the Pho/Gamma single-pinhole collimator which is directed at the thyroid isthmus. The patient must be positioned to remain stationary during the exposure.

ISOTOPE AND DOSE. Normally, 50  $\mu$ Ci of  $^{131}$ I iodide is given orally 6 to 24 hours prior to the study. Smaller doses may be used, depending upon radioiodide uptake. The 24-hour uptake is generally twice the 6-hour uptake and therefore permits data accumulation at double the rate. (Note: Thyroid scintiphotography may also follow oral or intravenous administration of  $^{99}$ mTc pertechnetate to yield higher data densities and good images of small nodules.)

DATA ACCUMULATION. With <sup>131</sup>l iodide, small cold nodules located within thyroid lobes may be defined by data densities as low as 5000 counts in the entire scintiphoto. Better resolution is produced in the image by longer counting times to accumulate an increased number of counts. Extended exposure times may also be necessary to obtain thyroid images in children who are given reduced isotope doses.

CASE HISTORY. The clinical illustrations on the facing page are for a patient with the following case history: Female, 53 years old. Scheduled for mitral-valve

surgery. Referred for thyroid evaluation because of atrial fibrillation and recent weight loss. Pertinent physical findings limited to a fine tremor and a 60-gram multinodular thyroid gland. Neck radioiodide uptake was 43% at 24 hours and TT<sub>4</sub> was 9.4  $\mu$ gm% (normal maximum 8.2  $\mu$ gm%). Initially, a rectilinear scan was ordered.

**EVALUATION.** The rectilinear scan was performed with the focal distance of the collimator carefully adjusted to the level of the thyroid gland. The images thus produced failed to show any clear definition of two discrete palpable nodules, which are shown, as palpated, in outlines superimposed on the images.

The Pho/Gamma scintiphoto study was therefore ordered, following the procedure described above. In the scintiphoto obtained from this study, a definite cold nodule is apparent. It is seen as a large area of decreased labelling laterally in the mid-portion of the more actively functioning tissue in the left lobe. Other areas of decreased labelling are seen in both lobes.

CONCLUSIONS. The Pho/Gamma thyroid-imaging technique illustrated here is most often used as a primary diagnostic method for the determination of regional thyroid function. It may be used as a secondary or supplementary method when rectilinear scanning fails to demonstrate the nature of a clearly palpable nodule. In the latter case, the scintiphoto made with the Pho/Gamma single-pinhole collimator often demonstrates cold nodules, even though they are not apparent on the scan. Pho/Gamma imaging generally requires one-third the time of a rectilinear scan of the same area.

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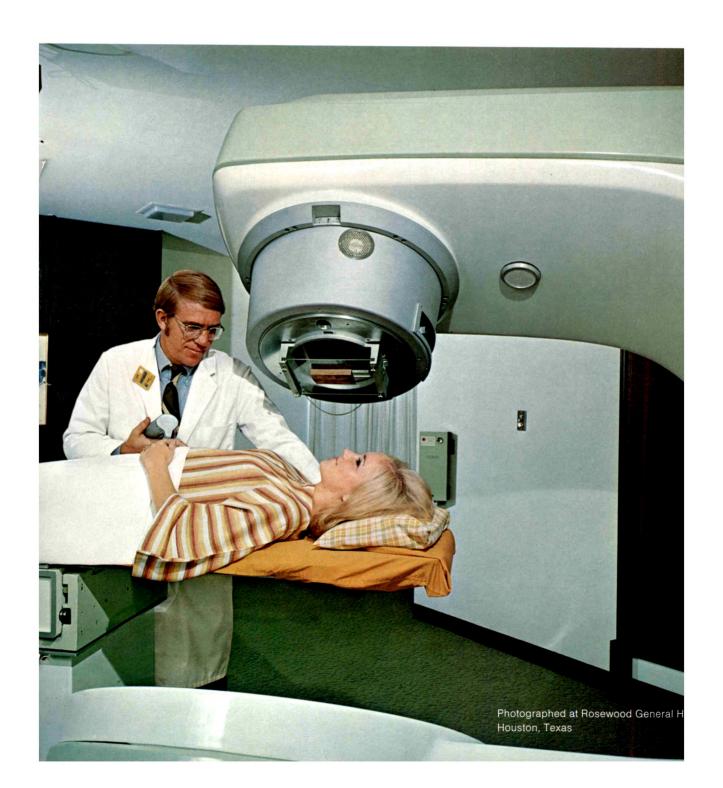
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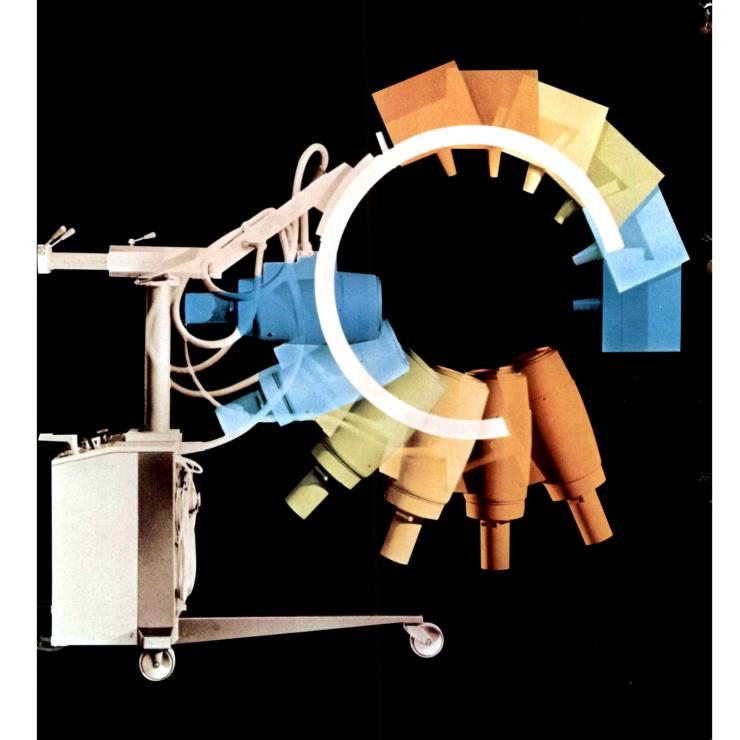
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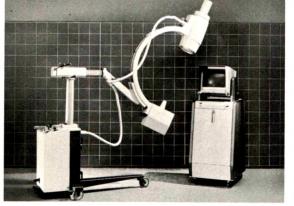
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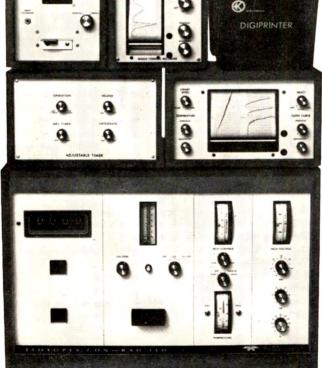
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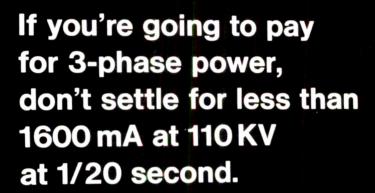
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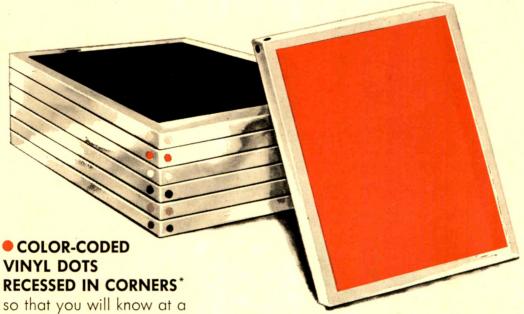


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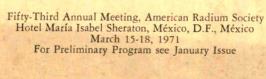
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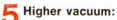




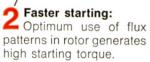
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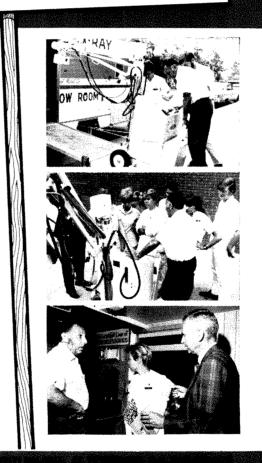
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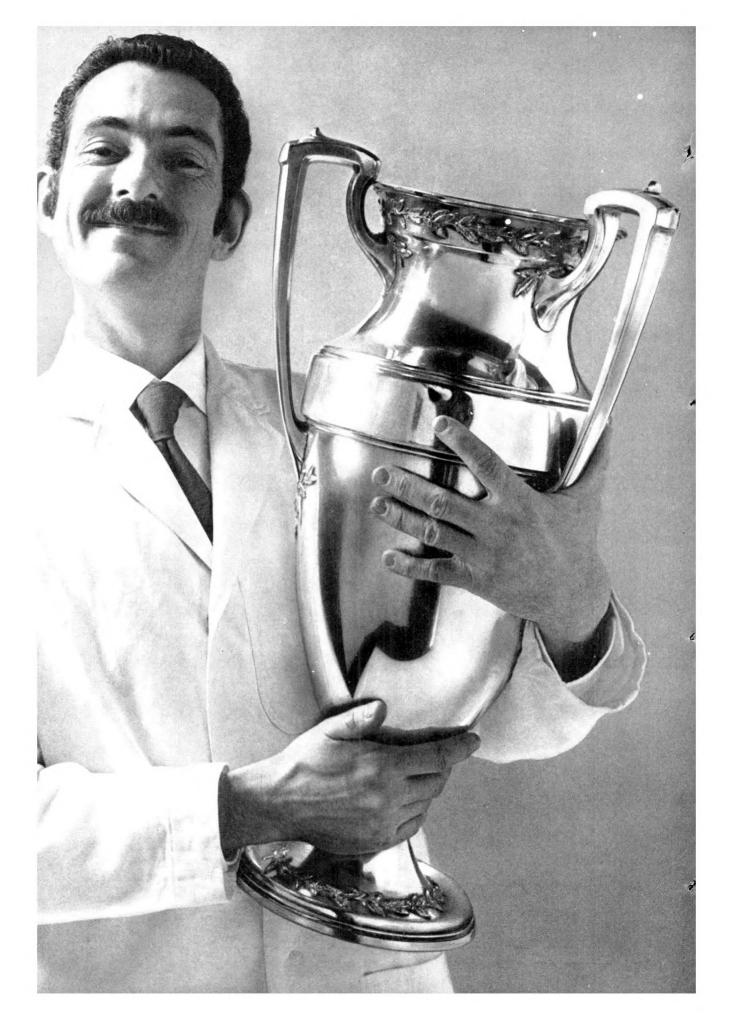
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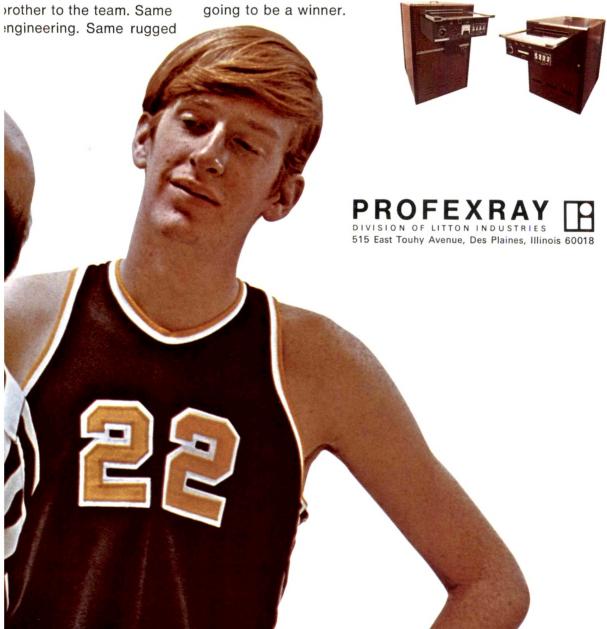
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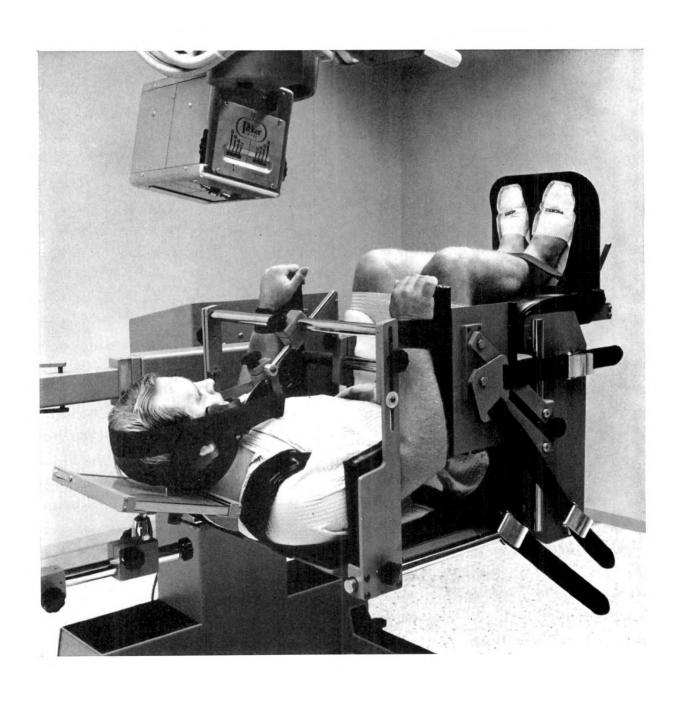
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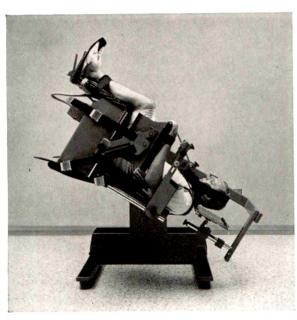
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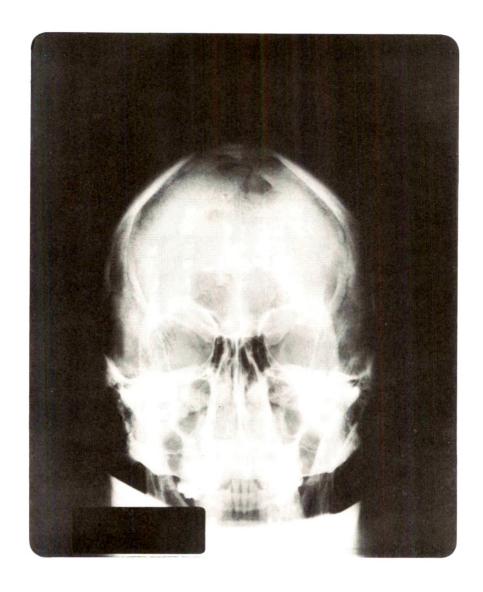


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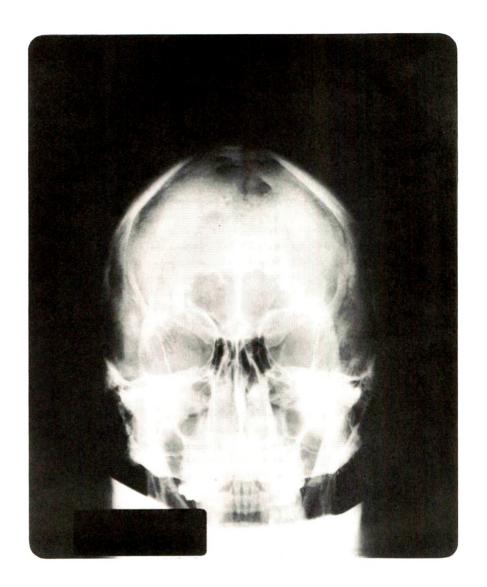


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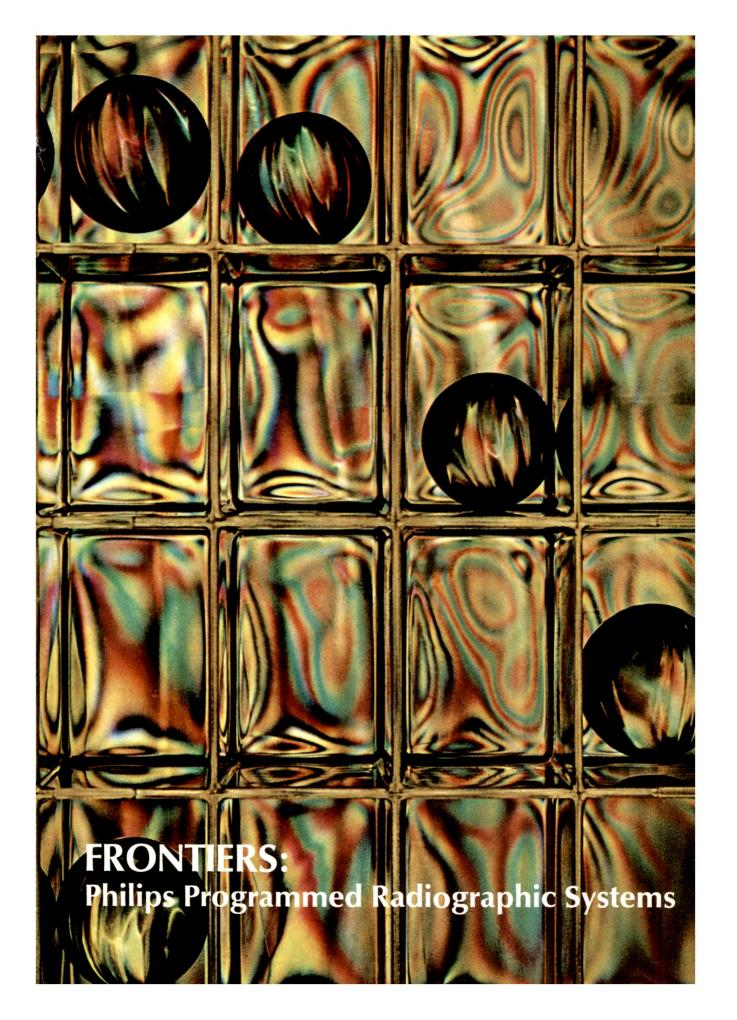
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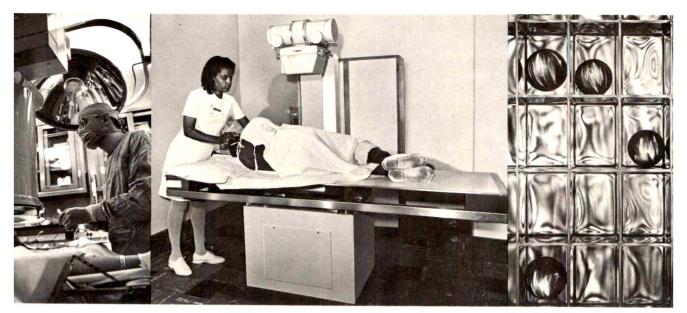


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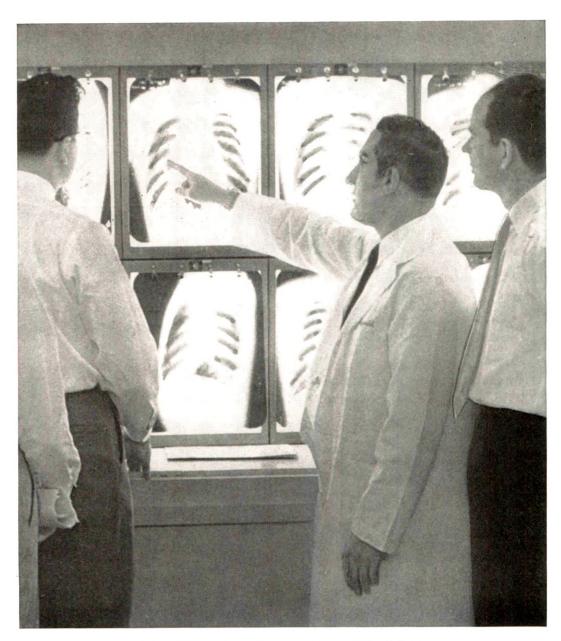
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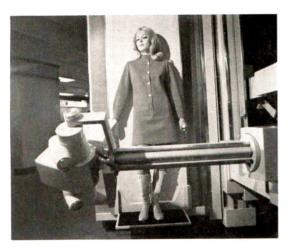
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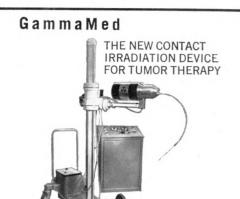


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1. Data on file at The Squibb Institute for Medical Research. See next page for brief summary.

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## Whenever drip infusion pyelography is indicated

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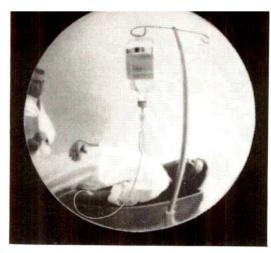
Contraindications: Contraindicated in persons hypersensitive to salts of diatrizoic acid. Urography is contraindicated in patients with anuria.

Warnings: A definite risk exists with the use of contrast agents in excretion urography in patients with multiple myeloma. There has been anuria with progressive uremia, renal failure and death. This risk of the procedure in these patients is not a contraindication; however, partial dehydration in preparation for study is not recommended since it may predispose for precipitation of myeloma protein in renal tubules. No therapy, including dialysis, has been successful in reversing this effect. Myeloma should be considered in persons over 40 before undertaking urographic procedures.

In cases of known or suspected pheochromocytoma, if the physician feels that the possible benefits outweigh the considered risks, radiopaque materials should be administered with extreme caution; however, an absolute minimum of material should be injected, the blood pressure should be assessed throughout the procedure, and measures for treating a hypertensive crisis should be available.

Contrast media may promote sickling in homozygous individuals when injected I.V. or intra-arterially. Although a history of sensitivity to iodine *per se* or to other contrast media is not an absolute contraindication, administration of meglumine diatrizoate requires extreme caution in such cases. Meglumine diatrizoate should be used in pregnant patients only when the physician deems its use essential to the welfare of the patient since safe use during pregnancy has not been established. Perform thyroid function tests prior to administration of meglumine diatrizoate since iodine-containing contrast agents may alter the test results. Perform urography with extreme caution in persons with severe concomitant hepatic and renal disease.

Precautions: Diagnostic procedures involving use of contrast agents should be performed under the direction of personnel with prerequisite training and a thorough knowledge of the particular procedure. Appropriate facilities should be available for coping with situations which may arise as a result of the procedure and for emergency treatment of severe reactions to the contrast agent itself; competent personnel and emergency facilities should be available for at least 30 to 60 minutes after I.V. administration since delayed reactions have been known to occur. These severe life-threatening reactions suggest hypersen-



sitivity to the contrast agent. A personal or family history of asthma or allergy or a history of a previous reaction to a contrast agent warrants special attention and may predict more accurately than pretesting the likelihood of a reaction although not the type nor severity of the reaction in the individual. The value of any pretest is questionable. The pretest most performed is the slow injection of 0.5-1.0 cc. of the preparation which may be given through the needle to be used for the full dose. If no reaction occurs within 15 minutes, the full dose may be given; however, this does not preclude the possibility of reaction. Should the test dose produce an untoward response, the necessity for continuing the examination should be reevaluated. If deemed essential, examination should proceed with all possible caution. In rare instances, reaction to the test dose may be extremely severe; therefore, close observation and facilities for emergency treatment are indicated.

Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by urographic agents; therefore, if known or suspected hepatic or biliary disorder exists, administration of meglumine diatrizoate should be postponed following the ingestion of cholecystographic agents. Consider the functional ability of the kidneys before injecting meglumine diatrizoate.

The recommended rate of infusion should not be exceeded. The diuretic effect of the drip infusion procedure may hinder an assessment of residual urine in the bladder. Adequate visualization may be difficult or impossible in uremic patients or others with severely impaired renal function (see Contraindications).

Adverse Reactions: Reactions most frequently encountered with drip infusion pyelography are nausea and urticaria. Chills, metallic taste, vomiting, dizziness, a rise or fall in blood pressure, itching, flushing, or generalized feeling of warmth, sneezing, etc. may occur and, rarely, may be severe enough to require discontinuation of dosage. Severe reactions which may require emergency measures (see Precautions) are a possibility and include cardiovascular reaction characterized by peripheral vasodilatation with hypotension and reflex tachycardia, dyspnea, confusion, and cyanosis progressing to unconsciousness. An allergic-like reaction ranging from rhinitis or angioneurotic edema to laryngeal or bronchial spasm or anaphylactoid shock may occur. Temporary renal shutdown or other nephropathy may occur. Intravenous injection of meglumine diatrizoate in a more concentrated formulation has produced a few instances of a burning or stinging sensation and of venospasm or venous pain.

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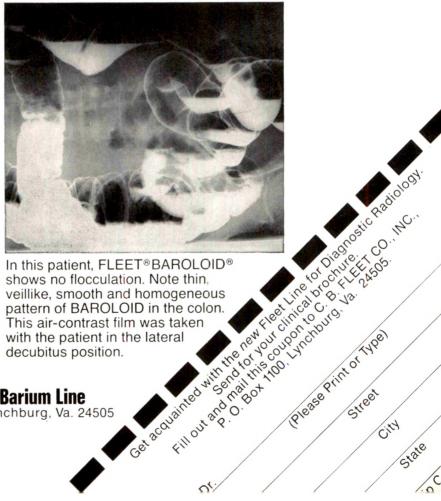
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\*Bryk, D. and Roska, J. C.: Radiology 92:832, Mar., 1969.



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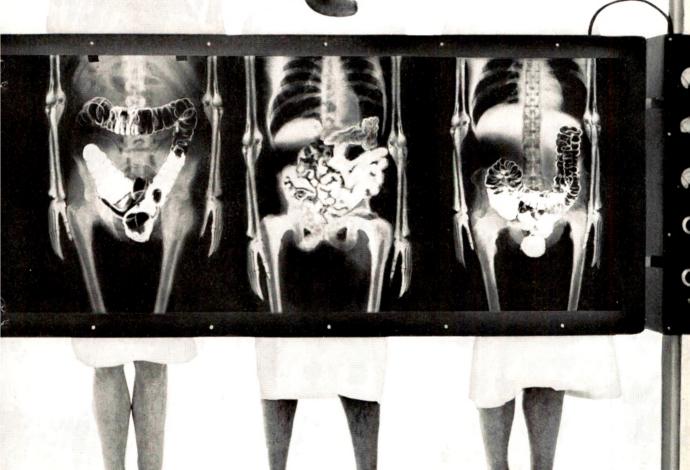
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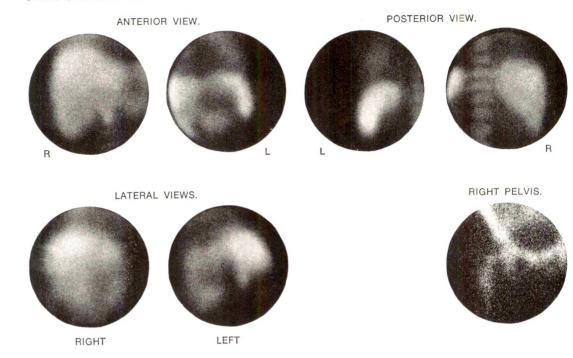
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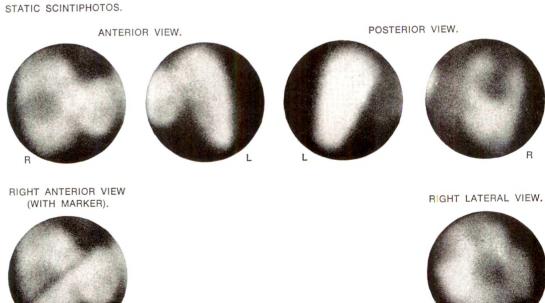
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## CASE STUDY NO. 1. CIRRHOSIS WITH FOCAL NECROSIS. STATIC SCINTIPHOTOS.



## CASE STUDY NO. 2. LEIOMYOSARCOMA METASTATIC TO LIVER. STATIC SCINTIPHOTOS.



# Th Liv r Study

## Evaluation of Reticuloendothelial System Labelling in the Liver with the Nuclear-Chicago Pho/Gamma® Scintillation Camera

Liver scintiphotography employing 99mtechnetium sulfur colloid and the Pho/Gamma Scintillation Camera offers extremely high resolution images of reticuloendothelial-system distribution in the liver, spleen and bone marrow.

PRELIMINARY DISCUSSION. In the normal liver, the reticuloendothelial system is uniformly distributed. with areas of decreased labelling showing only in the region of the porta hepatis, gall bladder fossa, and in intersegmental fissures.

Abnormal regional decreases of liver labelling may be recognized as either (1) irregular decrease of labelling in the whole liver or an area of it or (2) focal decreases of labelling with discrete margins and clear definition in comparable scintiphoto views.

SETTING-UP. Liver scintiphotography is usually best performed with the high-resolution, low-energy Pho/ Gamma collimator appropriate for 99mTc. The patient is positioned touching the collimator, and is examined in the recumbent position to reduce respiratory and other motions. In circumstances where the entire liver and spleen area are to be visualized in one view, the diverging collimator may be used.

ISOTOPE AND DOSE. An intravenous injection of 3 or 4 mCi of 99mTc sulfur colloid is administered.

DATA ACCUMULATION. Twenty minutes after injection, a series of static scintiphotos of the liver, spleen and bone marrow is obtained. A non-enlarged spleen is best imaged in left posterior and oblique views. Useful marrow views include upper sternal area, and left pelvis, hip and femur.

Data densities of 500,000 counts for an anterior view of the liver are desirable. Preset exposure time is kept constant throughout examination of the liver and spleen so that exposure intensity will be comparable in all the scintiphotos of these organs. For marrow scintiphotos, increased dot density and 2-minute exposures are normally used.

CASE HISTORIES. Case Study No. 1: Male, 60 years old. Known cirrohosis probably due to chronic alcoholism. Admitted for evaluation of low-grade fever.

Case Study No. 2: Female, 62 years old. Admitted for evaluation of abdominal cramping and liver enlargement. Seven years earlier, partial gastrectomy

yielded the diagnosis of "leiomyoma, ulcerated stomach." Two years prior to this admission, laparotomy had revealed leiomyosarcoma in the left lobe of the liver.

EVALUATION. The purpose of these Pho/Gamma liver studies is to evaluate (1) shape, position, and general outline of the liver as imaged on the scintiphotos and (2) the nature of any labelling decrease, whether uniform, irregular or focal. Labelling in the spleen and marrow is compared with liver labelling to assess the possibility of portal-systemic shunting (indicated by greater spleen and marrow labelling, relative to the liver) or hypertrophy of the bone marrow.

In the clinical scintiphotos shown at left, examples of uniform decreased labelling, irregular labelling, and focal defects of labelling are evident.

The patient with cirrhosis (Case Study No. 1) has generalized decrease and irregularity of labelling consistent with that disease. Furthermore, a focal defect of labelling exists in the left lobe of the liver and is best seen in the left lateral view. (This defect was subsequently found by local surgical biopsy to be the site of focal necrosis which had been responsible for the patient's low-grade fever of unknown origin.) Also typical of a cirrhotic are the bright labelling of the slightly enlarged spleen and bone marrow (with marrow extension into the right femur).

The patient with leiomyosarcoma (Case Study No. 2) is an excellent example of focal metastatic lesions causing some decrease of liver labelling, as well as enlargement of the liver that is so common with metastatic disease of the liver. Giant splenomegaly also exists on a congestive basis.

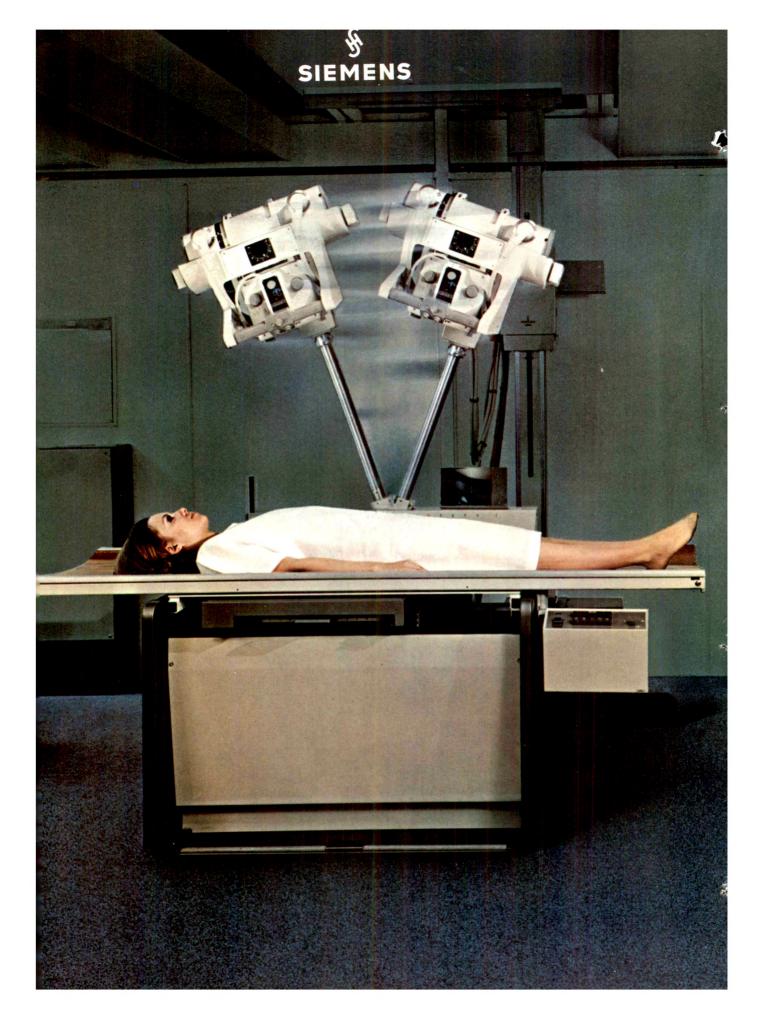
CONCLUSIONS. Liver scintiphotography with the Pho/Gamma Scintillation Camera and 99mTc sulfur colloid appears to be a markedly improved liverimaging technique and sensitive diagnostic test for liver disease.

This form of scintiphotography provides a large amount of specific information about liver structure and hemodynamics and is an accurate guide for the selection of biopsy sites. When combined with other special procedures, such as liver scintiphotography during rose-bengal excretion or liver-blood-flow evaluation, the Pho/Gamma liver study with 99mTc sulfur colloid offers many other diagnostic possibilities.

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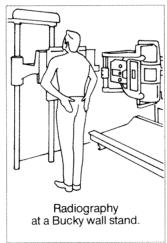
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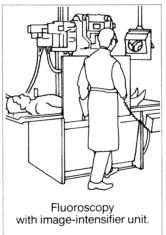
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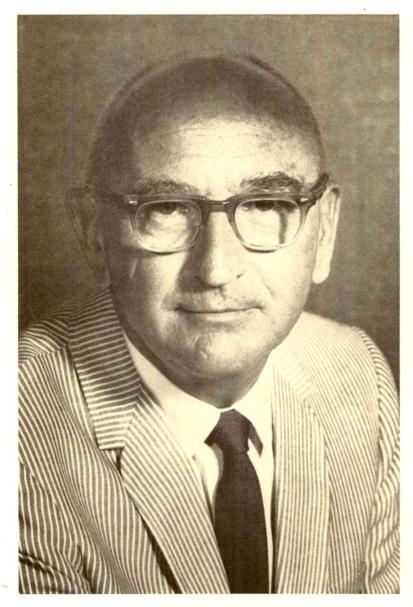
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# THE AMERICAN JOURNAL OF ROENTGENOLOGY RADIUM THERAPY AND NUCLEAR MEDICINE

Vol. III

FEBRUARY, 1971

No. 2

# CANCER OF THE UTERINE CERVIX\* JANEWAY LECTURE, 1970

By GILBERT H. FLETCHER, M.D. HOUSTON, TEXAS

CANCER of the uterine cervix is a fitting subject to honor Henry H. Janeway who, appointed Chief of Surgery at Memorial Hospital of New York City in 1915, was instrumental in promoting intracavitary radium therapy for the treatment of cervical cancer.

In 1919, Janeway published a comprehensive review of the results of surgery in 5,027 patients presenting with cancer of the cervix, with an 11.7 per cent salvage rate. I aneway was greatly impressed with the effectiveness of intracavitary radium therapy to control the local lesion, and considered it to be superior to surgical removal for borderline resectable tumors. However, he stated that a strong argument in favor of the radical abdominal operation was to provide the only approach by which lymphatic metastases could be removed, and he added that very few patients with involved lymph nodes had ever been cured.

This separate evaluation of the effectiveness of methods of treatment for the primary lesion and for the regional lymphatics is a central concept in cancer management.

Effective intracavitary radium therapy techniques, primarily those designed at the Curie Foundation and at the Radiumhemmet, resulted in improved survival rates by the mid 1920s. In 1927, Heyman<sup>22</sup> reported from several series of patients treated either surgically or by irradiation that the results in operable cases were 35 per cent either with surgery or with irradiation. Heyman commented that the surgical series included only patients whose disease had been resected, whereas the irradiated series included patients with undetected nonresectable disease because they had not had an abdominal exploration. This lack of comparability is still with us when we attempt to assess the results of surgery or radiation therapy in series of patients placed in the same clinical stages.

<sup>\*</sup> Presented at the Fifty-second Annual Meeting of the American Radium Society, Coronado Island, San Diego, California, March

<sup>1-5, 1970.</sup>From the Department of Radiotherapy, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas.

This investigation was supported by Public Health Service Research Grants Nos. CA-06294 and CA-05654 from the National Cancer Institute and Grant 2 Go3 RM-00007-02 from RMP of Texas.



Fig. 1. Radiation treatment failure. Patient, age 59, treated in 1950 for carcinoma of the cervix, Stage 1, with radium consisting of 2 applications 12 days apart for a total of 5,500 mg.-hr., and 1,600 r external radiation therapy given through 4 portals. A central recurrence occurred 34 months later. (Reproduced by courtesy of A. I. Sherman.<sup>39</sup>)

The French gynecologic surgeon, Jean-Louis Faure, conceded in 1928 that treatment for cancer of the uterine cervix was primarily radiotherapeutic. There was, however, continued use of the radical hysterectomy, the best known series being that of Victor Bonney who obtained a 40 per cent 5 year NED (no evidence of disease) rate in 500 patients undergoing surgical resection out of a total of 800 patients.5 The challenge of radiation treatment for uterine cervical cancer increased in the 1940s and the 1950s. Today the opinion is that either treatment is acceptable, and that one should individualize to suit the patient's situation.

In analyzing survival and control rates, we have the opportunity to review the progress made since 1919. On the basis of

clinical tumor biology and radiobiology established from quantitative clinical data, we can re-assess the fundamental concepts of radiation response, dosimetry, and combined irradiation and surgery.

## RADIORESISTANCE OF CANCERS OF THE UTERINE CERVIX

Sherman, 39 reviewing 21 central irradiation failures in patients treated at Washington University in St. Louis, showed that in 18 patients for whom radium localization roentgenograms were available, the radium geometry was extremely poor. One of his cases (Fig. 1) shows the vaginal radium lying anterior to the cervix, which results in areas of underdosage. Parenthetically, the dose at Point A might be optimal. With areas of underdosage in and around the cervix, failure to control the central disease can be anticipated, just as one would expect lack of surgical control of a lesion if there was a gross cut-through. Cold spots are sufficient to explain failures without seeking a biologic explanation. As in a surgical procedure, care must be applied to every detail of intracavitary radium therapy (Fig. 2, A and B).

logic radioresistance per se does not exist for epithelial tumors. Two factors which determine the potential for eradication of the disease are: (1) the number of tumor cells, and (2) the oxygenation of the tumor bed. A small fraction of hypoxic cells in a large population of cancer cells necessitates an enormous increase in tumor dose to eradicate the disease. There are data for squamous cell carcinoma of the upper respiratory and digestive tracts and for adenocarcinoma of the breast indicating that a high percentage of subclinical disease in the regional lymphatics can be eradicated<sup>3,15,29</sup> with doses of 4,500 to 5,000 rads in 5 weeks, whereas large masses at the primary site or in lymph nodes have a lower control rate

with much higher doses. In addition to the

number of cells and the oxygenation of the

tumor bed, there is a sigmoid response curve

The radiobiologic data established in the

last 10 to 15 years have shown that bio-

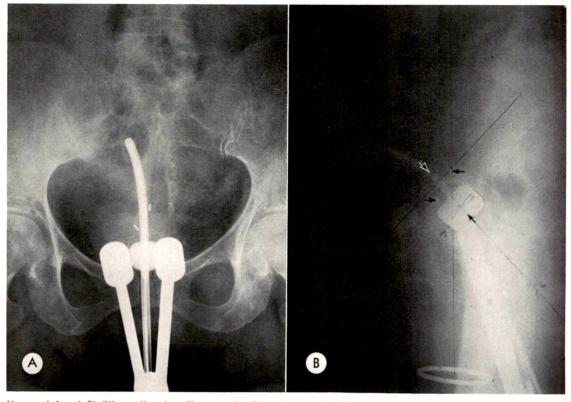


Fig. 2. (A and B) Silver clips (small arrows in B) are inserted with a radon seed inserter in the anterior and posterior lips of the cervix to determine the position of the colpostats to the cervix. A plane perpendicular to the radium system determined by the centers of the colpostats and the cephalad end of the endocervical source (large arrows) passes through the paracervical triangles and is taken for lateral throw-off calculations. (Reproduced by courtesy of G. H. Fletcher and F. N. Rutledge. Carcinomas of the uterine cervix. In: Modern Radiotherapy-Gynaecological Cancer. Butterworth & Co., Ltd., London. [In press].)

for tumors identical in size and composi-

An absolute cancerocidal dose does not exist. One must establish what dose is needed to eradicate microscopic disease in the lymphatics of the vaginal mucosa or parametria or small foci in regional lymph nodes and establish what dose is needed to control large masses. With intracavitary radium therapy, the distance from the sources to the peripheral extent of the disease is of paramount importance. The socalled radioresistance of adenocarcinoma of the cervix or of the endometrium is caused by invasion of the myometrium with cells at too great a distance from the radioactive sources to receive an adequate dose.

#### DOSIMETRY

Since the early 1920s, intracavitary radium therapy and external irradiation have been used. There have been considerable arguments throughout the years as to which should be applied first—external irradiation or intracavitary radium therapy —and even of whether external irradiation is of any value.1,32,33 In Figure 3 is shown an idealized volume distribution of combined external beam and intracavitary radium, expressed in threshold skin ervthema doses, for patients treated by Healy in 1924 at Memorial Hospital of New York City.21 This idealization of dosimetry on paper has been and remains a fallacy in the dosimetry of intracavitary radium therapy for cancer of the uterine cervix. In Figure 4,

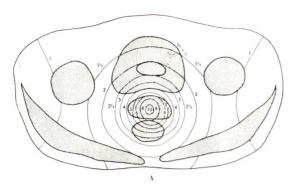


Fig. 3. Idealized combined radium and external roentgen dosage used in 1924 at Memorial Hospital of New York City for cancer of the cervix. The numbers represent threshold erythema doses. (Reproduced by courtesy of W. P. Healy. *Ann. Surg.*, 1931, 93, 451–459.)

A-F, are shown a number of clinical situations which distort the central geometry.<sup>38</sup> Determining dosage at a point in the paracervical area with reference to the radium system<sup>43,44</sup> is an illusory and damaging

practice. Although the importance of the inverse square law has been recognized from the early days of radiologic physics, it is strange that its consequences in brachy-radium therapy have been and still are overlooked by many. One is bound to have central failures if one first uses intracavitary radium therapy for large central lesions; there must be shrinkage of the volume of disease before radium can be used with effectiveness.

Because the T-shaped or linear arrangement of the radioactive sources results in a precipitous fall-off in dose from the surface of the applicators toward the periphery of the pelvis, there is no point or surface which is representative of an average tissue dose. The doses received by the pelvic organs and the regional lymphatics are dependent upon the length of the uterine cavity and the roominess of the vault, on the type of applicators, on the respective uterine and vaginal

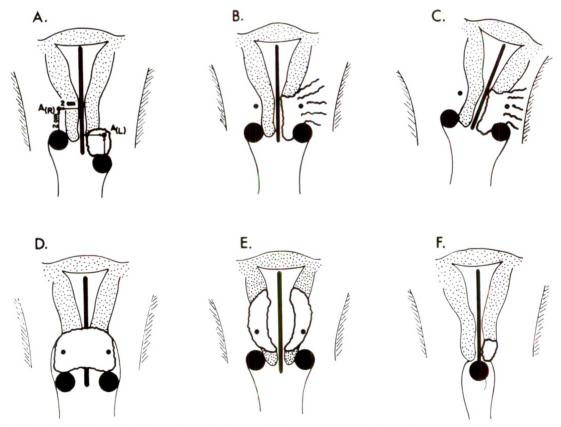


Fig. 4. (A-F) Clinical situations distorting the central geometry. (Reproduced by courtesy of G. Schwarz. 38)

 $Table\ I$   $carcinoma\ of\ the\ cervix$   $maxima\ for\ combining\ external\ irradiation\ and\ intracavitary\ radium\ therapy^{17}$ 

Stage	Whole Pelvis (rads)	Maximum Hours (1)	Maximum mghr. (1) (2)	Parametrial
I≤1 cm.		72—2 weeks—72	10,000	
I>1 cm.		72—2 weeks—72	10,000	3,000-4,000 rads
and H <sub>A</sub>	2,000	48—2 weeks—72 (3)	9,000	1,000-2,000 rads
	4,000	48—2 weeks—48	6,500	
П <sub>В</sub> *	4,000	48—2 weeks—48	6,500	a diamental and a second a second and a second a second and a second a
	4,000	48—2 weeks—48	6,500	1,000-1,500 rads or side involved
Ша	5,000	72 (4) or 48—2 weeks—24—48 (3)	5,000	Possibly 1,000 rads on side involved
Шв	6,000	72 (4)	4,000	
and IV	7,000			

(1) Use whichever maximum occurs first, either the time or the mg.-hr.

(2) May be exceeded in large radium systems if there is too large a separation or for unusual tumor size or location (e.g., posterior or anterior lip, etc.).

(3) May use the longer time first if the first application is unusually good and the second application may not be as good.

(4) If the status of central disease indicates it, the time may be increased beyond 72 hours or above 5,000 mg.-hr. Then split into 48 hours-2 weeks-24 to 48 hours.

Note: A tandem with a protruding source and a 3 cm, diameter vaginal cylinder should have a 20 mg, source in the cylinder with one and a half sources protruding. The loading is 15-10-20; 15-10-20, etc.

\* Whole pelvis irradiation may be carried to 5,000 rads if there is slow regression.

radium system resulting in too high a central dose. Following this experience, 2 sets of maxima were established to take into consideration the compactness of the radium system (Table 1). There is no simple formula which can be used for dosage determination of intracavitary radium therapy.

#### ANALYSIS OF RESULTS

Five year survival rates are important, but it is equally important, or perhaps more important, to know the causes of death; *i.e.*, central disease in or around the cervix, disease in the parametria or in the regional lymphatics, or distant metastases, or intercurrent disease. Until recently, only survival rates were reported in the literature. I am aware of only one old publication by Juliette Baud who, in 1954<sup>2</sup> reported the sites of failures in patients with Stage I

disease treated at the Curie Foundation from 1919 to 1947.

Attention must be directed separately to central failures and failures in regional lymphatics, since the solution of these problems is not the same. Table 11 analyzes central failures alone or in association with other sites in patients treated from 1954 through 1963. In patients with Stage 1 and IIA disease, the incidence of central failures is negligible. If one closely analyzes the central failures in Stage II, one sees that they essentially occur in the large central lesions (Table III).8 With megavoltage the incidence of central failures in the bulky lesions was diminished by half because whole pelvis irradiation given first produces sufficient shrinkage to make the subsequent intracavitary radium therapy effective.8 Even in those patients with distorted anatomy, central failures are rare.14 A small

Table II

CENTRAL ACTIVE DISEASE ALONE OR CONCOMITANT
IN OTHER SITES APPEARING WITHIN FIVE YEARS

MEGAVOLTAGE SERIES<sup>M</sup> September 1954–December 1963

Stage	Total Number of Patients Treated	Patients with Central Active Disease
I)		
$II_{\mathbf{A}}$	734	12 (1.5%)
$II_{\mathbf{B}}$	291	15 (5.0%)
$III_{\mathbf{A}}$	324	24 (7.5%)
$III_{\mathbf{B}}$	275	49 (17.0%)
IV	81	32 (39.0%)

percentage of patients treated with 4,000 rads to the whole pelvis followed by radium develop severe complications, 9,40 One can choose to have fewer complications with more central failures.26

The analysis of failures in the regional lymphatics is complex because of the ignorance of the extent of lymph node involvement at the initial and follow-up examinations. Fingers can detect only greatly enlarged obturator, uterosacral or low hypogastric lymph nodes. This ignorance of the lymphatic spread of the disease has

been one of the main reasons for the mythical theories regarding the radiosensitivity of lymph node metastases of squamous cell carcinoma of the uterine cervix.

The importance of the spread of the disease to the regional lymphatics was recognized by Wertheim who, in practicing the extended hysterectomy, removed enlarged and hard lymph nodes. 45,46 Wertheim was of the opinion that only large or hard lymph nodes contained cancer. A few of the patients who had positive lymph nodes treated by this partial lymphadenectomy were alive at 5 years.46 As stated at the beginning of the lecture, Janeway recognized the necessity of treating the lymph nodes and considered this the advantage of the radical abdominal operation. Leveuf and Godard in 1927 tried to combine the effectiveness of intracavitary radium for the primary lesion with a transperitoneal lymphadenectomy. They published only preliminary results and apparently did not pursue the matter.28 Bonney5 obtained a 20 per cent NED rate at 5 years when the lymph nodes were positive; this figure is essentially unchanged in all surgical series since reported. Primarily in this country a comparison has been made of the percent

TABLE III

STAGE II CENTRAL RECURRENCES
SEPARATED BY TYPE OF LESION AND TIME OF RECURRENCE<sup>8</sup>

Time of					Everting Exthout Lowe ent Involve	r Üterine	Barrel-Shaped Endocervical Lesion and/or Positive Endometrial Biopsy			
Recur- rence	Cent. Alone	Cent. +Reg.	Cent. ±Reg. +DM	Cent. Alone	Cent. +Reg.	Cent. ±Reg. +DM	Cent. Alone	Cent. +Reg.	Cent. ±Reg. +DM	
<5 Yr. (43)	2	5	2	2	6	10		7	9	
>5 Yr. (7)	5	I						I		
Total	15			18.			17			

Cent.=central; Reg.=regional; DM=distant metastases.

Note: (1) The majority of the central recurrences appearing early are in the central bulky lesions and the barrel-shaped or endocervical lesions and are associated with pelvic disease and distant metastases.

<sup>(2)</sup> The late vault recurrences occur in the nonbulky lesions, and are isolated failures.

age of lymph nodes involved when patients had primary surgery versus irradiation followed by lymphadenectomy, first by Taussig<sup>41,42</sup> and shortly after by Morton.<sup>30</sup> Both authors showed that the percentage of involved regional lymph nodes was clearly less in those patients having had previous irradiation than in those treated surgically. Despite this information, the general belief of gynecologic surgeons in the 1940s was that squamous cell carcinoma in lymph nodes could not be sterilized by irradiation. Several other series of combined treatment were reported later by Gorton from Sweden<sup>18</sup> and by Grav, Gusberg, and Guttmann from Delafield-Columbia.20 They confirmed that positive lymph nodes were found far less frequently after irradiation than after primary surgical treatment.

Kottmeier and Forssner<sup>27</sup> have published invaluable information from a small series of patients who had a laparotomy for various reasons and were found by biopsy to have positive lymph nodes. They were treated with the old Radiumhemmet technique which did not give more than 4,000 roentgens to the lymph nodes by combined intracavitary radium and external irradiation. Thirty per cent of the patients were alive and well 5 years or longer.

In order to obtain quantitative information on the radiation response of infested lymph nodes, Felix Rutledge and we undertook systematic studies. Initially, a trans-

TABLE IV

LYMPHADENECTOMY SERIES IN SQUAMOUS CELL CARCINOMA OF THE CERVIX: RANDOMIZED STUDY OF PATIENTS WITH POSITIVE LYMPH NODES<sup>36</sup>

STAGE I–STAGE III February 1957 through February 1960

Stage		No. of Positive Lymph Nodes	Per Cent	
I	30	I	3.3	
$\Pi_{\mathbf{A}}$	39	4	10.3	
$II_{B}$	25	5	20.0	
$III_{\mathbf{A}}$	23	4	17.4	
$III_{B}$	25	2	8.0	

#### TABLE V

INCIDENCE OF POSITIVE LYMPH NODES UP TO THE BIFURCATION OF THE AORTA IN SPECIMENS OF LYMPHADENECTOMY PERFORMED THREE MONTHS AFTER COMPLETION OF RADICAL IRRADIATION IN 148 UNSELECTED STAGE IIIA AND IIIB CASES<sup>11</sup>

April 1955 through February 1960

Positive Lymph Nodes	No.
Only within irradiated area (obturator,	
external iliac, hypogastric)	7
Only outside irradiated area	
(common iliac)	IO
Both within and outside irradiated area	II
Total	28 or 20%

peritoneallymphadenectomy was performed 3 months after completion of irradiation in 100 consecutive Stage III patients who were medically suitable for the operation. The incidence of positive lymph nodes in the regional lymphatics up to the bifurcation of the aorta was found to be 19 per cent.35 After this, a program of randomization of lymphadenectomy 3 months after completion of radiation was initiated in patients with Stages I, II and III disease. Table IV shows by stages the incidence of positive lymph nodes.<sup>36</sup> The incidence of positive lymph nodes is low in all stages, particularly in the Stage III patients, when compared with published data.<sup>19</sup> Few patients with positive lymph nodes were cured of their disease. At operation the positive lymph nodes were matted and wrapped around the vessels. It is, therefore, not surprising that no benefit could be obtained with such advanced disease.

A retrospective study using the roentgenograms of radium applications showed that the obturator, external iliac and hypogastric lymph nodes had received between 5,000 and 6,000 rads from combined radium and external irradiation.

### EXTENDED IRRADIATION OF LYMPHATICS

Table v shows the location of the positive lymph nodes along the regional lymphatics

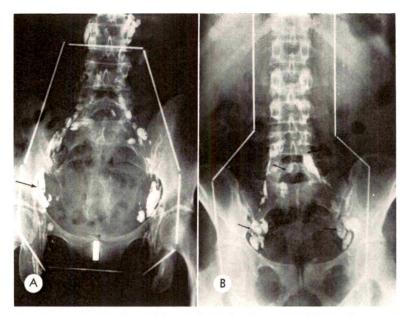


Fig. 8. Verification roentgenograms taken with simulator. (A) Extended fields to L-4 (17 to 20 cm. high) to include common iliac lymph nodes in a patient with Stage III<sub>A</sub> disease. Oblique lymphangiogram shows an involved external iliac lymph node at arrow. (B) Extended fields to level of diaphragm (8 cm. wide over paraaortic lymph nodes, 20 to 30 cm. high) to include paraaortic lymph nodes in a patient with Stage I disease. Arrows point to involved lymph nodes. (Reproduced by courtesy of G. H. Fletcher and F. N. Rutledge. Carcinomas of the uterine cervix. In: Modern Radiotherapy-Gynaecological Cancer. Butterworth & Co., Ltd., London. [In press].)

in the Stage III patients. One sees that of 28 patients, only 7 had disease limited to the irradiated area included in the 15 cm. high portals. We were aware that this portal size was not adequate to cover the common iliac lymph nodes, particularly when vaginal disease was extensive and the lower margin of the portals had to be low. This is the maximum practical field size with the 22 mev. betatron; furthermore, complications increase with volume. High doses to the whole pelvis were risky enough and baseline information had to be obtained. With the coming of a new generation of megavoltage generators which will permit large fields with 25 to 30 mev. optimal energy for parallel opposing portals, one can conceive of irradiating up to the level of L-4 when the obturator, hypogastric, and/or external iliac lymph nodes are positive and up to the diaphragm if the common iliac and/or paraaortic lymph nodes are positive (Fig. 8, A and B).

With interest in intensive irradiation of

the regional lymphatics, the knowledge of the dose delivered is important. With a computer program, the dose to points representative of the external iliac, common iliac, and low paraaortic lymph nodes can be obtained routinely (Fig. 9, A-D; and 10, A-D). The number of milligram hours in the radium system and the respective amounts of intrauterine and vaginal radium are separate factors in the contribution of dose to the regional lymphatics. The intrauterine radium is primarily contributory to the external iliac, hypogastric, and common iliac lymph nodes, whereas the obturator lymph nodes receive a significant contribution from the vaginal radium. The location of the radium system within the pelvis is another important factor. The intrauterine radium should be back and high between the common iliac lymph node chains. In the case shown (Fig. 10, A-D), the tandem has too much curvature. Kottmeier<sup>25</sup> and ourselves<sup>12</sup> became aware of this by direct measurement at laparotomy

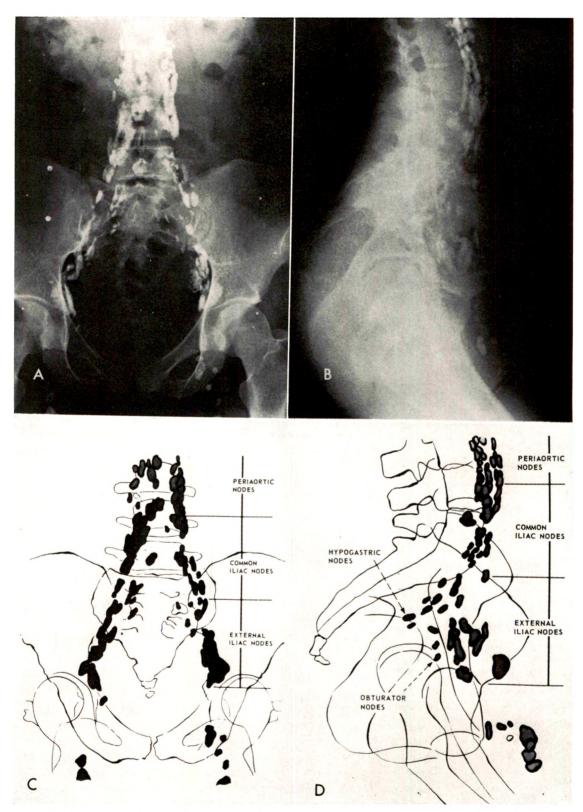
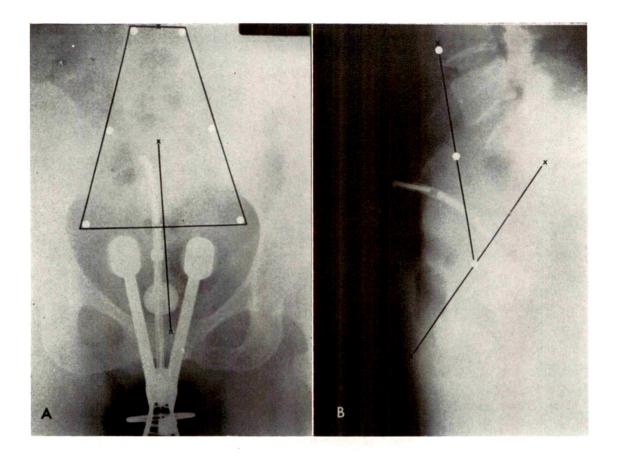


Fig. 9. (A) Anteroposterior and (B) cross-table lateral orthogonal roentgenograms of a patient with a normal lower extremity lymphangiogram. (C and D) The adjacent line drawings illustrate the regional lymphatics of the pelvis and lower lumbar area and the terminology used. With the exception of the obturator lymph nodes located inside of the acetabula, uterosacral lymph nodes and some of the hypogastric lymph nodes, the lymph nodes are not on the pelvic walls. (Reproduced by courtesy of F. Y. Durrance and G. H. Fletcher. Radiology, 1968, 91, 140–148.)



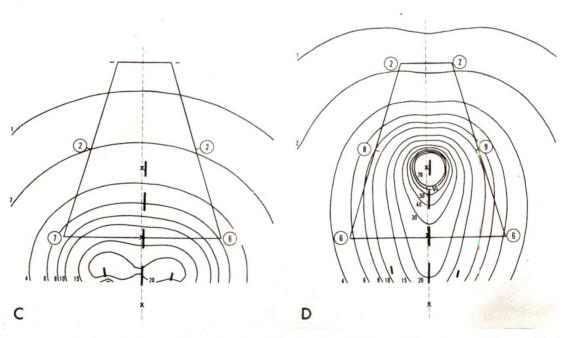


Fig. 10. (A-D) Intracavitary radium computer dosimetry for the external iliac, common iliac, and low paraaortic lymph nodes. The tandem has too much curvature and should be farther back for maximum contribution to the distant external iliac and common iliac lymph nodes. (Reproduced by courtesy of F. Y. Durrance and G. H. Fletcher. Radiology, 1968, 91, 140-148.)

of the dose to the lymph node areas with the radium in situ.

If one uses computer data to give a combined minimum dose of 5,500 rads to the external iliac and low common iliac lymph nodes, one must be aware of the location of the radium system. If it is in the hollow of the sacrum, as shown in Figure 11, then constrictive sigmoiditis can develop if excessive milligram hours are given to compensate for the increased distance from the radioactive sources to the lymph nodes.

Through the years a few patients without massive pelvic disease were found at laparotomy, performed for various reasons, to have positive paraaortic lymph nodes and were treated with portals to the diaphragm; 2 of these were NED more than 5 years. Furthermore, even if patients die from distant metastases, eradication of disease in the regional lymphatics diminishes the possibility of intractable pain from nerve involvement for which methods of alleviation are inefficient. Approximately 100 patients have had extended field treatment; a few have developed terminal ileitis in addition in constrictive sigmoiditis. This is to be expected with more ileum in the irradiated area. More time will be required to determine the incidence of ileitis, but it is probable that extended fields should not be used routinely, but only when lymphatic spread is demonstrated. Lymphangiograms are of value when positive and are indicated when there is a bulky lesion, be it Stage I or Stage II. I believe that the time has come, with the current negligible morbidity in exploratory laparotomy, to examine the lymphatics and remove palpable lymph node(s) without doing a true lymphadenectomy. Five thousand rads given in 5 weeks after the removal of large masses has a high chance to eradicate subclinical disease.

#### REDEFINITION OF CONCEPTS

I would like now to discuss with you some concepts which, I consider, are essential to the management of cancers of the uterine cervix.

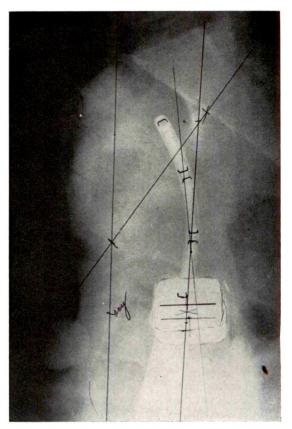


Fig. 11. Location of the radium system in the hollow of the sacrum in a patient who developed a constrictive sigmoiditis after 10,800 mg.-hr. and 4,000 rads to the parametria to deliver 5,500 rads to the distal external iliac and low common iliac lymph nodes

First, staging of cervical cancer needs to be rethought. Stage I cases range from a subclinical lesion, discovered at cone biopsy to be unquestionably invasive squamous cell carcinoma, to a lesion measuring 5 to 7 cm. in diameter with intact fornices and no palpatory evidence of disease in the parametria. This latter lesion would be staged T<sub>3</sub> or T<sub>4</sub>, if it were a squamous cell carcinoma of the oral cavity. A lesion minimally invading one fornix or with moderate parametrial infiltration should not be therapeutically grouped with a lesion which almost extends to one or both pelvic walls but is not fixed and therefore cannot be placed in Stage III.

I do not advocate changing the International Staging, but would favor adding

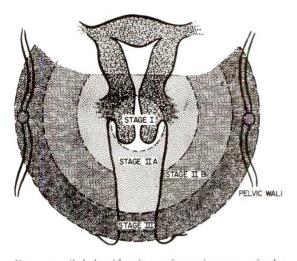


Fig. 12. Subclassification of carcinomas of the uterine cervix: Stage I, lesion limited to the cervix; Stage II<sub>A</sub>, involvement limited to vagina and/or slight parametrial involvement; Stage II<sub>B</sub>, involvement of the lateral aspects of the parametria, with or without vaginal involvement; Stage III<sub>A</sub>, involvement of one pelvic wall or lower third of vagina; Stage III<sub>B</sub>, involvement of two pelvic walls or of one pelvic wall and lower third of vagina. (Reproduced by courtesy of G. H. Fletcher, M. Stovall, and V. Sampiere from: Carcinoma of the Uterine Cervix, Endometrium, and Ovary. Year Book Medical Publishers, Inc., Chicago, 1962, p. 73.)

a substaging which takes into consideration the volume of cancer (Fig. 12). One must treat a patient according to her particular situation and not treat the stage; the interplay between intracavitary radium and external irradiation in Stage I, Stage II<sub>A</sub> and Stage II<sub>B</sub> patients is shown in Table VI. Some Stage I patients can be treated with considerable success by intracavitary radium alone; onversely, a few patients with Stages I and II<sub>A</sub> disease required 5,000 rads or more to the whole pelvis for various reasons.

Some patients with bulky lesions had an extrafascial conservative hysterectomy after 4,000 rads whole pelvis irradiation and 4,000 to 5,000 mg.-hr. in 1 application, instead of the usual 6,000 to 6,500 mg.-hr. in 2 applications. It was not without a measure of trepidation that Felix Rutledge used a conservative procedure rather than the accepted cancer operation. The radical

TABLE VI
STAGES I AND II CARCINOMA OF THE CERVIX
VARIATIONS IN RADIATION TECHNIQUE
September 1954 through June 1966

		Stage	
	Ι	$\Pi_{\mathbf{A}}$	$\Pi_{\mathrm{B}}$
Radium only	123	19	5
Radium+Parametrial Irradiation	283	137	19
<1,500 rads whole pelvis	4	3	I
2,000 rads whole pelvis	81	128	23
3,000 rads whole pelvis	8	17	I 2
4,000 rads whole pelvis	46	114	254
5,000 rads whole pelvis	3	I	14
6,000 rads whole pelvis	Ι	4	48
>6,500 rads whole pelvis	0	I	I
Totals	549	424	377

hysterectomy had been associated with prohibitive complications after intensive irradiation. Table VII shows the indications for which the extrafascial hysterectomy was performed; local control is excellent with central failure in only 2 of 87 patients with unfavorable bulky or endocervical barrel-shaped lesions. Theoretically, this combination may not be an accepted cancer procedure, but it has been successful in practice.

A close look shows that this approach is not actually a combination of two half measures but combines one method effective against certain areas of spread of the disease and the other method effective for another direction of spread. Four thousand rads to the whole pelvis, even if followed by diminished intracavitary radium, gives 8,000 to 10,000 rads to the vaginal mucosa and delivers to the lateral parametria, obturator, and external iliac lymph nodes at least 5,000 rads, which is effective for

TABLE VII

EXTRAFASCIAL HYSTERECTOMY AS PART OF THE PRIMARY TREATMENT OF STAGES I AND II SQUAMOUS CELL CARCINOMA OF CERVIX<sup>8</sup>

110/1,341 PATIENTS

1948-December 1963

	Indication for Hysterectomy								
Status	Bulky or Endocervical Barrel-Shaped	Pregnancy	Incomplete Radiation Therapy	Other: Fibroid Pyometria					
NED>3 Yr.	61/87	7/7	6/8	7/8					
Dead	26/87	0/7	2/8	1/8					
Central Failures	Central+PD	0	0	Central or Necrosis+PD					

NED= no evidence of disease; PD= disease in the pelvis and/or regional lymphatics.

small aggregates of cancer cells in these areas. The extrafascial hysterectomy removes disease in the myometrium which, despite some shrinkage after 4,000 rads to the whole pelvis, is still at too great a distance from the radium source to receive an effective dose (Fig. 13). This combination of the effectiveness of irradiation for subclinical disease with a conservative surgical procedure for removal of gross masses will, I believe, have many applications in the management of other cancers in the coming decade.

From a 5 year survival rate of 11.7 per cent, as reported by Janeway in 1919, to the present 5 and 10 year survival rates (Table VIII), significant progress has been made. As shown in Maryland by our President, Fernando Bloedorn, a network of cooperating clinics can make available highly effective modern radiotherapy to every woman with carcinoma of the cervix.<sup>4</sup>

The 2 previous Janeway lectures devoted to cancer of the uterine cervix, by Henry Schmitz in 1938<sup>37</sup> and by Frederick O'Brien in 1946,<sup>31</sup> brought up to date the progress made at those 2 points in time. Since then there has been not only technologic improvement but clarification of the fundamentals underlying the radiation therapy of cancer of the uterine cervix. We

understand better the effect of size, growth pattern, and mode of spread on the control rates.

The quality of survival should be given

TABLE VIII

SURVIVAL RATES FOR SQUAMOUS CELL

CARCINOMA ON INTACT UTERUS<sup>16</sup>

1,705 PATIENTS\*

September 1954 through December 1967

Stage	Five Year Survival Rate† Per Cent Megavoltage	Ten Year Survival Rate Per Cent Megavoltage
I	91.5	90.0
$II_{\mathbf{A}}$	83.5	79.0
$\mathrm{II}_{\mathrm{B}}$	66.5	57.0
$III_{\mathbf{A}}$	45.0	39.5
$III_{B}$	36.0	30.0
IV	14.0	14.0
CAF	RCINOMA OF CERVICA 189 PATIENTS	L STUMP
I	97.0	97.0
$\Pi_{\mathbf{A}}$	93.0	89.0
$\mathrm{H}_{\mathrm{B}}$	67.0	67.0
$III_{A}$	61.0	61.0
$\Pi_{\mathrm{B}}$	32.0	32.0
IV	0	0

<sup>\*</sup> Includes patients treated incompletely or for palliation.

<sup>†</sup> Modified life table method.

Patients dying from intercurrent disease are excluded.

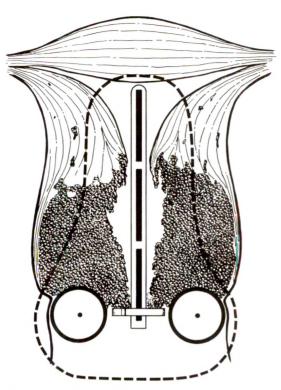


Fig. 13. With invasion of the myometrium of the isthmus (barrel-shaped lesion), tumor cells are too far for adequate contribution from the radium sources. Even after 4,000 rads, shrinkage may not be sufficient for disease in the periphery of the myometrium to be close enough to the radium sources. (Modified from: G. H. Fletcher. Textbook of Radiotherapy. Lea & Febiger, Philadelphia, 1966, p. 479.)

increased emphasis. Early cancers of the uterine cervix are probably overtreated either surgically or by irradiation in the attempt to obtain the highest possible survival rates; it is at the expense of increased morbidity and some measure of sequelae to all patients. This is true in several areas of cancer management today. Increased communication between the surgeon and the radiotherapist will bring the controversy over the treatment of choice to an intellectual level, with both members of the team taking an ecumenical approach to eliminate barriers and prejudices.

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#### ANALYSIS OF THE TREATMENT OF STAGE I AND STAGE II CARCINOMAS OF THE UTERINE CERVIX\*

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THE respective place of intracavitary radium (gamma ray therapy) and external irradiation in treatment for cancer of the uterine cervix has been debated since the mid 1920s when 200 kv. equipment became available. The purpose of this study is to show how these two modalities are combined in Stage I and Stage II cases to fit the extent of the disease and the local anatomy and not to treat with idealized planning based on staging.

Stage I disease includes all invasive carcinomas of the cervix, ranging from small lesions to very large lesions which are still confined to the cervix. Stage II cases can be substaged into Stage IIA (extension limited to the upper vagina and/or medial portions of the parametria) and into Stage IIB (lateral parametrial involvement, with or without massive central lesion occupying more than half of the true pelvis). A particular variety are the barrel-shaped lesions resulting from endocervical cancers invading the myometrium of the isthmus. This substaging has been used in the Gynecology Section of M. D. Anderson Hospital before the FIGO substaging.

Five year survival rates have been published. The sites of failures by treatment technique will be compared at the 2 year cut-off, because disease rarely appears locally in the pelvis or regional lymphatics<sup>18</sup> after this period of time.

The analysis of complications will be limited to those patients treated solely with radiation therapy. A clinical study has shown that adding lymphadenectomy with or without hysterectomy drastically increased the incidence and severity of complications and has been abandoned.1,9

#### CLINICAL MATERIAL

Between September 1954 and June 1966, 1,350 patients with Stage I and Stage II squamous cell carcinomas and adenocarcinomas of the uterine cervix on an intact uterus were treated at The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston. Thirty of the 1,350 patients had adenocarcinoma. There were 320 patients who had, as planned treatment, a surgical procedure combined with radiation therapy. Most surgical procedures were lymphadenectomy with or without hysterectomy. Most patients who had a surgical procedure were treated during 1957 to 1960 in a clinical trial to investigate the benefits of lymphadenectomy after a full course of radiation therapy.

Treatment planning for carcinoma of the cervix has been outlined in previous publications.4.7 In general, intracavitary radium therapy alone was used for favorable Stage I and selected Stage IIA lesions if the local anatomy was suitable for effective radium therapy and there was no complicating condition. Intracavitary radium therapy with parametrial irradiation was used for most of the Stage I and IIA lesions unless there was bulky or asymmetric disease or narrow vaginal vaults, often seen in elderly women; in this latter group of patients, whole pelvis irradiation was given prior to intracavitary radium therapy.4,5 Patients with Stage IIB disease usually received 4,000 rads whole pelvis irradiation

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prior to intracavitary radium therapy. Patients who received more than 4,000 rads usually had extensive disease or the patient's anatomy made intracavitary radium therapy impossible. Because adenocarcinomas grow locally with less lymphatic involvement, less whole pelvis irradiation and more intracavitary radium therapy was used. In bulky lesions, an added extrafascial hysterectomy has been used in the plan of treatment.

Tables I, II, and III show the different combinations of intracavitary radium and external irradiation for Stage I, Stage II<sub>A</sub> and Stage II<sub>B</sub>. External irradiation doses that were not an exact thousand were assigned to the closest thousand. Only 3 patients received more than 6,500 rads whole pelvis external irradiation.

The majority of patients with Stage I disease have been treated by intracavitary radium therapy plus parametrial irradiation. The patients who received more than 3,000 rads whole pelvis were those complicated by pregnancy, poor anatomic geometry and/or large central lesions. There are 4 Stage I patients who received more than 5,000 rads whole pelvis irradiation. One patient had a 10 cm. cervical mass diagnosed during the third trimester of pregnancy; after a cesarean section, the patient received essentially whole pelvis irradiation. One patient had to have a hypogastric ligation for massive vaginal bleeding; lymph node disease was found, but the case was not restaged according to the rules of clinical staging. One patient, poorly suited for general anesthesia because of jaundice, was given only one intracavitary radium application followed by whole pelvis irradiation. The fourth patient was a 73 year old senile patient with a large endocervical mass associated with a narrow vault which made effective radium treatment impossible.

The Stage IIA patients who received intracavitary radium therapy only had either small favorable portio lesions with minimal forniceal involvement or were senile and debilitated, necessitating short-

cuts. Approximately one-third of Stage IIA patients with small local lessons moderately involving the fornices or the medial parametria received intracavitary radium and parametrial irradiation. Those patients who received 1,500 to 4,000 rads whole pelvis had bulky central lesions, whole pelvis irradiation being given to diminish the bulk of the lesions before intracavitary radium.

There were 6 patients with Stage II. lesions with large central lesions, or very poor anatomy for radium, or complicating factors, who received more than 5,000 rads whole pelvis irradiation.

Most of the Stage IIB patients received 4,000 rads or more whole pelvis irradiation. Few patients had less whole pelvis irradiation with more intracavitary radium and parametrial irradiation. Five patients had radium only because of severe physical impairments or other malignancies, the treatment being essentially palliative in intent.

#### RESULTS

The sites, type and outcome of active disease are categorized as:

Central disease. Central disease is defined as clinical or biopsy evidence of persistent or recurrent disease either on the cervix, in the body of the uterus, or in the upper two-thirds of the vagina. Patients who had vaginal bleeding of any degree during the terminal phase of their disease were coded as having recurrent central disease.

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Regional disease. Disease anywhere in the pelvic structures or in the regional lymphatics, including common iliac lymph nodes, is categorized as regional disease. Patients with active disease in the parametrium and/or the regional lymphatics have the characteristics of sciatic pain, leg edema, hydronephrosis, and, at times, palpable pelvic masses.

Distal metastases. Distal metastasis is disease occurring outside the region designated as regional and/or local disease. The diagnosis of involved distal lymph

# Table I CARCINOMA OF THE CERVIX

STAGE I NED at Two Years (September 1954–June 1966)

			Dead										
Treatment	No. of Patients			NED	Local Only	Local+ Regional ±DM	Regional ±DM	DM	ID	Complica- tion of Radiother- apy	Complica- tion of Radiother- apy+Sur- gery	Un- known	Disease Salvaged by Surgery
Radium Only	123	117			2	1	3						
Radium+Para- metrium	283	262		2	9	3	2	I		4			
<1,5∞ rads WP	4	4											
2,000 rads WP	81	70		I	4	3	2	I					
3,000 rads WP	8	6			*****	2							
4,∞∞ rads WP	46	42		1	I	2							
5,000 rads WP	3	3				***************************************							
6,∞∞ rads WP	I	I								***************************************			
>6,500 rads WP				····									

NED=no evidence of disease; DM=distant metastases; ID=intercurrent disease; WP=whole pelvis.

nodes, such as in inguinal or supraclavicular regions, is made by palpation and biopsy. Distal metastases are manifested as progressive multiple parenchymal pulmonary nodules, mediastinal widening, hilar adenopathy, osseous destruction, nodular enlarged liver, ascites, etc. On occasion, positive paraaortic lymph nodes, liver metastases, or involvement of other abdominal organs were found at the time of laparotomy.

Intercurrent disease. Patients were reported dead from a medical disorder (including other primary cancers) other than the cervical malignancy.

Dead from complications of radiation. These patients died as a result of complications after treatment which consisted of irradiation only.

Dead from complications of radiation plus surgery. These patients died as the result of complications following treatment which included irradiation and surgery as the primary plan.

Unknown. This category was used in those cases for which available information was insufficient to allow a definite statement about the activity of the disease before death.

Tables 1. 11. and 111 show the number of patients free of disease and the causes of death according to stage and treatment categories at the 2 year follow-up. One patient with Stage IIB disease died of central active disease only. Twenty-two patients died with central active disease associated with regional disease or distant metastases. This excellent local control is obtained in patients with bulky central lesions and/or poor anatomy.5 An added extrafascial hysterectomy as part of the treatment contributes to the excellent local control in the patient with barrelshaped lesions.3 There were 3 patients with central recurrence alone or with regional disease who were salvaged by a subsequent surgical resection. Similar excellent control is obtained in the adeno-

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## Table II carcinoma of the cervix

#### STAGE IIA NED at Two Years (September 1954–June 1966)

						]	Dead					
Treatment	No. of Patients		NED	Local Only	Local+ Regional ±DM	Regional ±DM	DM	ID	Complication of Radiotherapy	Complica- tion of Radiother- apy+Sur- gery	Un- known	Disease Salvaged by Surgery
Radium Only	19	16			I		2					
Radium+Para- metrium	137	115		ĭ	6	7	8					
<1,5∞ rads WP	3	3										
2,000 rads WP	128	106		I	9	6				5	1 (V)*	
3,000 rads WP	17	16			I							
4,000 rads WP	114	85		2	14	7	4			2		
5,∞0 rads WP	1				1							
6,0∞ rads WP	4	3				1						
>6,500 rads WP	1	ī										

<sup>\*</sup> V = central disease.

## Table III CARCINOMA OF THE CERVIX

#### STAGE 11B NED at Two Years (September 1954–June 1966)

Treatment	No. of Patients	NED	Dead								
			Local Only	Local+ Regional ±DM	Regional ±DM	DM	ID	Complica- tion of Radiother- apy	Complica- tion of Radiother- apy+Sur- gery	Un- known	Disease Salvaged by Surgery
Radium Only	5	2		1			1	I			
Radium+Para- metrium	19	13			2	3	I			-	
<1,5∞ rads WP	1	1									
2,000 rads WP	23	16			3	3	1				
3,000 rads WP	12	4		2	I	4	I				
4,000 rads WP	253	190		13	22	16	6	1	3	ı	1 (V+PD)*
5,∞ rads WP	14	8			2	3	I				
6,∞∞ rads WP	48	29		6	2	4	4	ı		I	1 (V+PD)*
>6,500 rads WP	2		I						I		

<sup>\*</sup> V+PD=central and regional lymphatic disease.

carcinomas; extrafascial hysterectomy is used in the bulky lesions.<sup>10</sup>

In the Stage I and Stage IIA patients treated with intracavitary radium alone, there were few regional lymphatics failures showing that, in early lesions, regional lymphatics involvement is uncommon, not justifying external irradiation.

Table IV lists the complications by severity. Eighty-eight patients had mentionable complaints of which 54 were significant. Twenty-two of the 54 significant complications required either a correction by a surgical procedure or remained permanent.

Seventeen of these 22 severe complications were in patients who received 4,000 rads or more whole pelvis irradiation, usually because of bulky disease. There are also 2 or perhaps 3 severe complications caused by overtreatment. Other factors associated with complications are: old age, uncontrolled diabetes, cystocele, poor anatomy and markedly anteflexed uteri prior to the use of afterloading tandems. A narrow vault allows only a compact radium system, giving a high local dose. The use of a protruding source with an afterloading tandem in a narrow vault resulted in an overdose at the level of the posterior fornix, and some rectal ulcers did appear.12 Five patients developed partial hydronephrosis caused by fibrosis.<sup>11</sup>

#### SUMMARY

The irradiation treatment of patients with cancer of the uterine cervix, Stage I or Stage II, cannot be standardized. Considerable radicalism has to be used to control massive cancers. One could perhaps diminish the incidence of severe complications, which is not prohibitive being approximately 2 per cent, but more patients would die from uncontrolled cancer.

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Table IV

All complications

30 Stage 1 and 11 Treated with Irradiation Only

1,030 Stage I and II Treated with Irradiation Or	ıly
(September 1954–June 1966)	

Type of Complications	No. of Patients
Mentionable complaints of any kind Significant complications	88
in the 88 patients Severe complications in	54
the 88 patients (fistulae, sigmoiditis, ileitis, fatal vault necrosis, ileocon-	22
duit for bilateral hydro- nephrosis)	(17 with ≥4,000 rads whole pelvis irradia- tion)

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# POST-IRRADIATIONAL RECURRENT EPIDERMOID CARCINOMA OF THE UTERINE CERVIX\*

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RECURRENT cancers of uterine cervix can manifest in a variety of ways. The manner of clinical presentation and prognosis of this condition vary depending on the previous treatment, and the initial status of the primary cancer and of the patient.

Because of the general nihilistic attitude towards recurrent cervical cancers, very little attention has been paid to this disease process and its management. There is a dearth of information on this affection. Sporadic publications have appeared in the literature on its treatment during the past two decades or so.

It is the purpose of this paper to describe, in brief, the clinical manifestation and prognosis of recurrent epidermoid carcinoma of the uterine cervix following radiotherapy in an unselected series, and the results of re-irradiation or surgery dependent on site of recurrence and initial clinical stage.

#### MATERIAL AND METHOD

During 1920 through 1953, there were 4,308 cases of epidermoid carcinoma of the uterine cervix treated primarily with radiotherapy at the Roswell Park Memorial Institute. There were 90 other patients who were excluded because of employment of surgery or of no treatment. All patients were staged according to the 1950 League of Nations criteria<sup>7</sup> from information recorded in the hospital records.

#### RADIOTHERAPY OF PRIMARY CANCER

Treatment methods varied considerably

between periods before and at or after 1940. During the early period radon seeds (500-1,500 mg.-hr. of emitted dose) were commonly implanted into the cervix and/or vaginal portion of the cancer before radium and/or roentgen ray therapy was administered. The 200 or 250 kv. units with a half value layer (HVL) filtration of 0.5, 1.0 or 2.0 mm. of Cu were employed to deliver approximately 1,600 r to the midline of pelvis within I week. An anterior and posterior arrangement of portals measuring 15×15 to 20×20 cm. was used. Radium was usually administered with a tandem or a tandem and plaque applicator, delivering emitted doses close to 4,000 mg.hr. Dose to Point A was estimated to be roughly 6,500 r and that to Point B roughly 2,000 r. The contribution of dose from radon seeds was not included.

After 1940 the use of radon seeds was almost completely dispensed. The cervical and/or vaginal portion of the tumor was treated with radium usually in 2 tubes attached at right angles to one end of the tandem and less often with tandem and intravaginal colpostats or plaques. External therapy was administered more often through a 4 field crossfire arrangement of portals measuring 10×15 to 10×20 cm. and less often by the 6 field technique. The 400 kv. unit having a filtration of 5.0 mm. Cu HVL was commonly employed except in obese patients who were treated on the I mev. unit. Radiation dosage from roentgen rays and radium sources varied depending on clinical stage of cancer.

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Stage I or II lesions were treated with a full pelvic roentgen ray dose of approximately 4,000 r in 4 weeks and radium emitted dose of approximately 4,500 mg.hr. Dose to point A was estimated to average approximately 8,700 r and that to point B 4,500 r. Some of the radiation techniques used for local or regional disease during this period have been described elsewhere.<sup>10</sup>

### FOLLOW-UP EXAMINATION

Routine clinical examinations were undertaken at I to 3 month intervals during the first 2 years, at 6 months during the next 3 years, and at yearly intervals, after 5 years post-treatment. Roentgenograms of the chest, complete blood cell counts and urinalysis were generally obtained at 6 to 12 month intervals or as found necessary. Other roentgenologic studies (intravenous pyelography, barium enema examination, bone survey), as well as cystoscopy and sigmoidoscopy were done as indicated by the clinical findings. Histopathologic and/ or cytologic tests were carried out as found necessary and feasible. A 99.4 per cent follow-up was maintained at 5 years and 98.2 per cent at 10 years. Survival rates corrected for deaths due to other causes were estimated by the method of Berkson and Gage.

### RECURRENCE OF CANCER

The occurrence of clinical recurrence was defined arbitrarily as follows: (1) there must have been at least a 6 month interval of complete clinical healing between initial treatment and the time of detection of recurrence; (2) there must have been a minimum of 2 consecutive follow-up examinations which failed to detect evidence of disease; and (3) the histology of the recurrent lesion, when available, must have been the same as that of the initial cancer. Histologic or cytologic confirmation of recurrent cancer was available in 32 per cent of all cases, 67 per cent for cervical and/or vaginal, and 21 per cent for pelvic or distant recurrent lesions. Tissue specimens

of the latter were usually obtained in cases with associated central lesions.

The anatomic sites of recurrence were categorized into those occurring locally in cervix, vagina or both. Local lesions extending into parametria (including pelvic wall) or lesions recurrent in parametria only were grouped as pelvic recurrences. Distant ones included cases with disease beyond the true pelvis with or without findings of local or pelvic disease.

According to the above criteria there were 1,165 cases with suspected recurrent cancer. However, sufficient information was not available in the form of literal descriptions or of anatomic diagrams in the records of 14.3 per cent of recurrent cases.

### TREATMENT OF RECURRENT CASES

There were no standard radiation techniques for treatment of recurrent lesions. Treatment of cases were individualized depending on the general conditions of patients, tolerance of their irradiated tissues, and previous radiation treatment factors. Pure cervical recurrences were often managed with a radium applicator (R.P.M.I., tandems or cylinders) employing usually 2,500 to 5,000 mg.-hr., depending on the size of lesion. External therapy was sometimes added. Cases with vaginal recurrence were treated with radium in cylinder, delivering a I cm. depth dose of 4,000-6,000 r, or with an implant of radon seeds or needles to deliver a minimum dose of 4,000-6,000 r. Parametrial lesions were treated with full pelvic or hemipelvic irradiation of approximately 2,000 to 4,000 r in 3 to 4 weeks as tolerated. When such lesions were associated with central lesions, radium application and/or radon seed implants were administered. Treatments had to be discontinued in approximately 10 per cent of the cases with local or pelvic recurrence. Patients with distant metastases were treated palliatively.

### RESULTS

Table I shows that the distribution of patients treated for primary cancer during

carcinomas; extrafascial hysterectomy is used in the bulky lesions.<sup>10</sup>

In the Stage I and Stage IIA patients treated with intracavitary radium alone, there were few regional lymphatics failures showing that, in early lesions, regional lymphatics involvement is uncommon, not justifying external irradiation.

Table IV lists the complications by severity. Eighty-eight patients had mentionable complaints of which 54 were significant. Twenty-two of the 54 significant complications required either a correction by a surgical procedure or remained permanent.

Seventeen of these 22 severe complications were in patients who received 4,000 rads or more whole pelvis irradiation, usually because of bulky disease. There are also 2 or perhaps 3 severe complications caused by overtreatment. Other factors associated with complications are: old age, uncontrolled diabetes, cystocele, poor anatomy and markedly anteflexed uteri prior to the use of afterloading tandems. A narrow vault allows only a compact radium system, giving a high local dose. The use of a protruding source with an afterloading tandem in a narrow vault resulted in an overdose at the level of the posterior fornix, and some rectal ulcers did appear.12 Five patients developed partial hydronephrosis caused by fibrosis.11

### SUMMARY

The irradiation treatment of patients with cancer of the uterine cervix, Stage I or Stage II, cannot be standardized. Considerable radicalism has to be used to control massive cancers. One could perhaps diminish the incidence of severe complications, which is not prohibitive being approximately 2 per cent, but more patients would die from uncontrolled cancer.

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TABLE IV

ALL COMPLICATIONS

1,030 Stage 1 and 11 Treated with Irradiation Only

(September 1954–June 1966)

Type of Complications	No. of Patients
Mentionable complaints of any kind Significant complications in the 88 patients Severe complications in the 88 patients (fistulae, sigmoiditis <sup>3</sup> , ileitis, fatal vault necrosis, ileocon- duit for bilateral hydro- nephrosis)	88  54  22  (17 with ≥4,∞∞ rads whole pelvis irradiation)

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# POST-IRRADIATIONAL RECURRENT EPIDERMOID CARCINOMA OF THE UTERINE CERVIX\*

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RECURRENT cancers of uterine cervix can manifest in a variety of ways. The manner of clinical presentation and prognosis of this condition vary depending on the previous treatment, and the initial status of the primary cancer and of the patient.

Because of the general nihilistic attitude towards recurrent cervical cancers, very little attention has been paid to this disease process and its management. There is a dearth of information on this affection. Sporadic publications have appeared in the literature on its treatment during the past two decades or so.

It is the purpose of this paper to describe, in brief, the clinical manifestation and prognosis of recurrent epidermoid carcinoma of the uterine cervix following radiotherapy in an unselected series, and the results of re-irradiation or surgery dependent on site of recurrence and initial clinical stage.

### MATERIAL AND METHOD

During 1920 through 1953, there were 4,308 cases of epidermoid carcinoma of the uterine cervix treated primarily with radiotherapy at the Roswell Park Memorial Institute. There were 90 other patients who were excluded because of employment of surgery or of no treatment. All patients were staged according to the 1950 League of Nations criteria<sup>7</sup> from information recorded in the hospital records.

### RADIOTHERAPY OF PRIMARY CANCER

Treatment methods varied considerably

between periods before and at or after 1940. During the early period radon seeds (500-1,500 mg.-hr. of emitted dose) were commonly implanted into the cervix and/or vaginal portion of the cancer before radium and/or roentgen ray therapy was administered. The 200 or 250 kv. units with a half value layer (HVL) filtration of 0.5, 1.0 or 2.0 mm. of Cu were employed to deliver approximately 1,600 r to the midline of pelvis within I week. An anterior and posterior arrangement of portals measuring 15×15 to 20×20 cm. was used. Radium was usually administered with a tandem or a tandem and plaque applicator, delivering emitted doses close to 4,000 mg.hr. Dose to Point A was estimated to be roughly 6,500 r and that to Point B roughly 2,000 r. The contribution of dose from radon seeds was not included.

After 1940 the use of radon seeds was almost completely dispensed. The cervical and/or vaginal portion of the tumor was treated with radium usually in 2 tubes attached at right angles to one end of the tandem and less often with tandem and intravaginal colpostats or plaques. External therapy was administered more often through a 4 field crossfire arrangement of portals measuring 10×15 to 10×20 cm. and less often by the 6 field technique. The 400 kv. unit having a filtration of 5.0 mm. Cu HVL was commonly employed except in obese patients who were treated on the I mev. unit. Radiation dosage from roentgen rays and radium sources varied depending on clinical stage of cancer.

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Stage I or II lesions were treated with a full pelvic roentgen ray dose of approximately 4,000 r in 4 weeks and radium emitted dose of approximately 4,500 mg.-hr. Dose to point A was estimated to average approximately 8,700 r and that to point B 4,500 r. Some of the radiation techniques used for local or regional disease during this period have been described elsewhere.<sup>10</sup>

### FOLLOW-UP EXAMINATION

Routine clinical examinations were undertaken at 1 to 3 month intervals during the first 2 years, at 6 months during the next 3 years, and at yearly intervals, after 5 years post-treatment. Roentgenograms of the chest, complete blood cell counts and urinalysis were generally obtained at 6 to 12 month intervals or as found necessary. Other roentgenologic studies (intravenous pyelography, barium enema examination, bone survey), as well as cystoscopy and sigmoidoscopy were done as indicated by the clinical findings. Histopathologic and/ or cytologic tests were carried out as found necessary and feasible. A 99.4 per cent follow-up was maintained at 5 years and 98.2 per cent at 10 years. Survival rates corrected for deaths due to other causes were estimated by the method of Berkson and Gage.

### RECURRENCE OF CANCER

The occurrence of clinical recurrence was defined arbitrarily as follows: (1) there must have been at least a 6 month interval of complete clinical healing between initial treatment and the time of detection of recurrence; (2) there must have been a minimum of 2 consecutive follow-up examinations which failed to detect evidence of disease; and (3) the histology of the recurrent lesion, when available, must have been the same as that of the initial cancer. Histologic or cytologic confirmation of recurrent cancer was available in 32 per cent of all cases, 67 per cent for cervical and/or vaginal, and 21 per cent for pelvic or distant recurrent lesions. Tissue specimens

of the latter were usually obtained in cases with associated central lesions.

The anatomic sites of recurrence were categorized into those occurring locally in cervix, vagina or both. Local lesions extending into parametria (including pelvic wall) or lesions recurrent in parametria only were grouped as pelvic recurrences. Distant ones included cases with disease beyond the true pelvis with or without findings of local or pelvic disease.

According to the above criteria there were 1,165 cases with suspected recurrent cancer. However, sufficient information was not available in the form of literal descriptions or of anatomic diagrams in the records of 14.3 per cent of recurrent cases.

### TREATMENT OF RECURRENT CASES

There were no standard radiation techniques for treatment of recurrent lesions. Treatment of cases were individualized depending on the general conditions of patients, tolerance of their irradiated tissues, and previous radiation treatment factors. Pure cervical recurrences were often managed with a radium applicator (R.P.M.I., tandems or cylinders) employing usually 2,500 to 5,000 mg.-hr., depending on the size of lesion. External therapy was sometimes added. Cases with vaginal recurrence were treated with radium in cylinder, delivering a 1 cm. depth dose of 4,000-6,000 r, or with an implant of radon seeds or needles to deliver a minimum dose of 4,000-6,000 r. Parametrial lesions were treated with full pelvic or hemipelvic irradiation of approximately 2,000 to 4,000 r in 3 to 4 weeks as tolerated. When such lesions were associated with central lesions, radium application and/or radon seed implants were administered. Treatments had to be discontinued in approximately 10 per cent of the cases with local or pelvic recurrence. Patients with distant metastases were treated palliatively.

### RESULTS

Table I shows that the distribution of patients treated for primary cancer during

Table I
RECURRENT EPIDERMOID CARCINOMA OF UTERINE CERVIX ACCORDING TO PERIOD OF TREATMENT
OF PRIMARY CANCER
CLINICAL DATA ITEMS

		Period of Treatment					
	1920–1939	1940–1953	1920-1953				
No. of Primary Cases	2,145	2,163	4,308				
Clinical Stage, per cent							
I	10.2	21.9	16.3				
II	25.7	39.2	32.3				
III	38.7	27.1	32.8				
IV	25.4	11.9	18.6				
Survival Rate, per cent*							
5 Year	36.1	56.2	46.I				
10 Year	32.5	53.I	42.8				
Persistence, No. (per cent)	914 (42.5)	505 (23.4)	1,419 (32.9)				
Recurrence, No. (per cent)	597 (27.6)	568 (26.2)	1,165 (26.9)				
Site of Recurrence, per cent							
Cervix	40.2	34.2	37.5				
Vagina	11.2	9.5	10.3				
Vagina and Cervix	1.3	3.4	2.4				
Pelvis	29.0	21.2	<b>24.</b> 7				
Distant	5.1	16.2	10.8				
Unknown	13.2	15.5	14.3				
5 Year Survival Rate*	16.7	11.8	15.1				

<sup>\*</sup> Survival rate of cancer deaths only.

periods 1920–1939 and 1940–1953 is nearly equal. Initial clinical stage is more advanced, survival lower and the proportion of cases with persistent cancer higher in the early period than in the latter; however, the incidences of recurrent lesions are about the same in both groups. Local and pelvic recurrences occurred more frequently and distant ones less frequently in the early period. Sites of recurrences were indeterminate in 14.3 per cent of cases, being nearly of the same proportion for both periods. It is interesting to note that the over-all 5 year survival rate after detection of recurrence is higher in the former period.

Figure 1 illustrates the time course of detection of recurrence beginning at 6 months and ending at 9 years post-therapy. Nearly 75 per cent of recurrences are detected by 2 years after which the rate of detection is gradual, reaching 100 per cent at the 9th year. The mean time was approximately 11 months: 9 months for

the early period and 13 months for the latter. It should be mentioned here that a small percentage of recurrences continued to appear after this time interval. However, we chose to end the observation period for recurrences at 9 years for reason of minimum 5 year follow-up time for evaluation of results of retreatment.

Cervical recurrences are detected early. This is followed by vaginal (includes also those with both cervical and vaginal re-

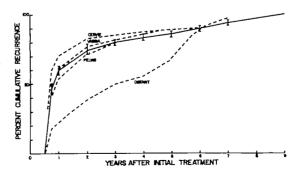


Fig. 1. Time course of detection of recurrence.

Table II

SEQUENCE OF CLINICOPATHOLOGIC FINDINGS IN THE DETECTION OF RECURRENT CARCINOMA

OF THE UTERINE CERVIX

CLINICOPATHOLOGIC FINDINGS

		Order of Findings								
	First	Second	Third	Fourth	Fifth					
		Per Cent of Columns								
Positive Biopsy*	3	31	63	70	67					
Gross Tumor	20	27	21	0	o					
Bleeding	30	5	r	0	0					
Discharge	19	18	2	0	0					
Pain in Pelvis	10	6	2	11	0					
in Back	3	3	I	3	0					
in Leg	4	3	4	3	0					
Swelling of Leg	3	4	3	11	33					
Other Findings	8	3	3	3	0					
No. of Cases	1,165	745	187	29	3					
Per Cent of Cases	100	64	16	2.5	0.03					

<sup>\* 32</sup> per cent were confirmed by positive biopsy or smears.

currences) and then by pelvic recurrences. Distant ones are detected at a much slower rate in a time course independent from the others.

Table II shows the order in which recurrent cervical cancer manifested. Thirty-

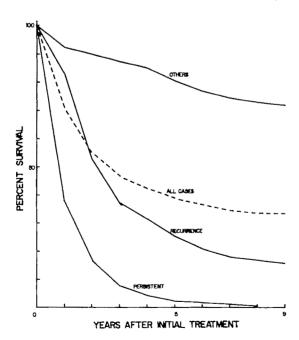


Fig. 2. Crude survival curves of patients with persistent, recurrent and no cancer.

six per cent had I clinicopathologic finding, 48 per cent had 2. Symptomatically vaginal bleeding and/or discharge was the first most common finding. Twenty-three per cent had no symptoms and recurrences were diagnosed by detection of gross tumor or by biopsy. Pain in pelvis, leg or back or swelling of leg are less frequent symptoms. Symptoms become less frequent at the second or greater order of presentation, and gross tumor or biopsy becomes more frequent. By the third order most patients have already been diagnosed as having had recurrent cancers.

Figure 2 shows the crude survival curves of patients with recurrent, persistent and no cancer. The over-all survival curve is shown in a dotted line. The 5 year rates are 25, 3, 82 and 40 per cent, respectively. The curve of patients that died without recurrence or persistence is approximately 10 per cent lower at 9 years than the one for females in New York State adjusted for age.

Table III shows the incidence, time of detection, site of recurrence, per cent reirradiated cases and results of treatment of recurrent cancers in relation to initial clinical Stages I to III, initial treatment

Table III

RECURRENCE OF EPIDERMOID CARCINOMA OF CERVIX AFTER INITIAL IRRADIATION ACCORDING
TO STAGE AND PERIOD OF TREATMENT AND RESULTS OF RE-IRRADIATION

						· · · · · · · · · · · · · · · · · · ·	
	Initial Clinical Stage						
Clinical Data Item/Period		I		I	III		
	1920-39	1940-53	1920-39	1940-53	1920–39	1940-53	
No. of Primary Cases Roentgen Dose (average) Milligram Hours (average) Survival Rate Per Cent*	212 1,650 4,100	47° 3,5∞ 5,1∞	534 1,600 4,100	842 3,100 4,700	806 1,700 4,200	583 4,500 3,700	
5 Years 10 Years Recurrence, No. (per cent) Time of Recurrence	79 75 56 (25)	82 78 100 (21)	54 50 189 (35)	61 58 256 (30)	33 29 247 (31)	43 40 154 (25)	
<2 Years 2-5 >5	62 29 9	35 39 26	64 25	47 32 21	68 24 8	57 28 15	
Site of Recurrence, Per Cent Cervix Vagina	50	44	44	36	38	30	
Vagina and Cervix Pelvis	1 0 23	3 3 22	6 1 26	10 3 21	13 2 30	10 4 25	
Distant Unknown Pairmediated Coase Pan Coase	1 25	20 8	9 14	15	5 12	15 16 62	
Re-irradiated Cases, Per Cent 5 Year Survival Rate* Complications, No. (per cent)	95 36 4 (7)	79 21 18 (18)	88 28 14 (7)	70 11 17 (7)	90 12 9 (4)	62 7 16 (10)	

<sup>\*</sup> Survival rates of cancer deaths only.

factors and survival for the 2 periods treatment of primary disease. The total dose delivered by external therapy was less for the early period. The emitted dose from radiation sources was slightly less in this period; however, it was approximately the same if the contribution of radon seeds was included. The survival rates are the same for Stage I lesions, but they are higher for more advanced stages with parametrial extensions in the later period.

The proportion of recurrent cases, as well as the rate of recurrence is less, and that of recurrences at distant sites is greater in the later period. Radiotherapy was employed less often in this period due to the more frequent use of other modalities of treatment. For example, cordotomy, alcohol block, colostomy, and urinary diversionary procedures were used for palliation more frequently during the later period. The

higher salvage rate observed in the early period in Table I is maintained when the cases are subdivided according to stage. For Stages II and III this rate is twice that in the later period.

The complication rates are somewhat higher in the later period, especially in Stages I and III groups. Most complications were those of proctitis and cystitis. Rectal complications were more frequent during the later period and bladder ones more frequent during the early period. Most of these symptoms subsided during the period of study; however, some of them persisted or recurred at later time intervals. Chronic proctitis occurred in 16 cases, chronic cystitis in 14, and both in 3. Vesicovaginal fistula presented in II and rectovaginal ones in 9 cases, making an incidence of fistulas in 9.5 per cent of cases alive at 5 years.

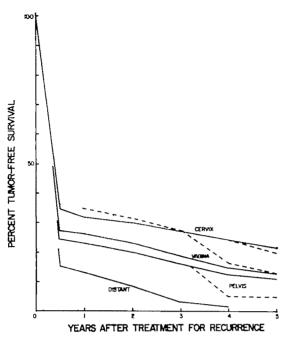


Fig. 3. Time course of survival in patients with recurrent cancer.

Figure 3 illustrates the time course of survival in patients with recurrent cancers. As expected, cases with less advanced degrees of recurrences have better salvage rates. The 5 year tumor-free rates for cervical, vaginal, pelvic and distant sites of recurrences are 23, 13, 11 and o per cent, respectively. Histologically or logically, confirmed recurrent lesions in cervix or vagina have similar rates to those diagnosed clinically or pathologically 5 years; however, at earlier times such vaginal lesions have rates equal to the cervical ones. Rates of pathologically confirmed pelvic recurrences fall parallel to those of the clinically diagnosed ones until 3 years post-therapy. Sample sizes for pathologically confirmed vaginal and pelvic recurrences were too small to yield reliable figures.

Table IV shows the 5 year results according to initial Stages I to III and sites of recurrences for the 2 periods. It is seen that generally at each level of stage and of cervical recurrences or of others involving the pelvic structures, rates are

better in the early period than in the later period.

Table v shows the results of retreatment of selected cases who had a course of radiotherapy or of radical surgery for recurrences following irradiation of initially Stage I or II lesions during 1940-1953. There were 41 patients managed with radium alone, 90 with roentgen rays alone, 22 with roentgen ray and radium, 32 with seeds with or without roentgen rays, and 11 with radical surgery (hysterectomy and lymph node dissection in 8 and exenteration in 3). A staging scheme somewhat equivalent to the International one was devised in order to categorize cases of recurrent cervical cancers for the purpose of treatment comparison. For example, recurrent Stage IIA means cancer recurrent in upper two-thirds of vagina or in upper two-thirds of vagina and in cervix, recurrent Stage IIB means cancer recurrent in parametria but not fixed to the pelvic wall with or without cervical or upper two-third vaginal involvement or with both. Cases are subdivided according to recurrent and initial stages for each of the treatment groups.

The over-all result of retreatment by

Table IV

PROGNOSIS OF IRRADIATED PATIENTS ACCORDING TO SITE OF RECURRENCE, STAGE AND PERIOD OF INITIAL TREATMENTS

and the second s		I	Anatom	c Site		
Initial Stage	Period	Cervi	c Only	Vagina or Pelvis		
		No.	(per cent)	No.	(per cent)	
I	1920-39 1940-53	43 34	(28)* (38)	20 9	(15) (23)	
II	1920-39 1940-53	34 16	(84) (76)	16 10	(60) (67)	
III	1920-39 1940-53	17 9	(82) (44)	11	(109) (45)	

<sup>\* 5</sup> year survival rate of cancer deaths only.

Table V

RESULTS OF TREATMENT IN SELECTED CASES OF RECURRENT EPIDERMOID CARCINOMA

OF THE UTERINE CERVIX

1940–1953

Recurrent	Initial			Roentgen ray		Roentgen ray +Radium		Radon Seeds +Roentgen ray		Radical Surgery	
Stage*	Stage	No.	(per cent)†	No.	(per cent)	No.	(per cent)	No.	(per cent)	No.	(per cent)
I	I	67 28	(9)† (14)	63	(11)	50 25	(2) (4)	25 33	(4) (18)	88	(8)‡
IIA	II	20 30	(5) (10)	100	(2) (2)	25	(1)	33	(3)	100	<u> </u>
IIB	II	J-	— —	44 11	(16) (35)	0	(1) (3)	0	(2) (2)	0	(I) (I)
III	I II	۰	(3)	0	(3)		(3)	0	(3)		
Total	I+II	34	(41)	23	(00)	18	(22)	16	(32)	73	(11)
Type of Compliant Chronic Proctition	s	ı	(2)§	5	(6)	2	(9)	2	(6)		
Chronic Cystitis Bladder Fistula Rectal Fistula	3	I	(2)	5	(7) (6)	3	(14) —	I	(3)	1	(9)
All Fistulas		3	(5) (7)	5 10	(11) (6)	I	(5) (5)	I	(3)	I	(9)

Patients were selected on the basis that each had completed a planned course of treatment.

\* Extent of recurrent cancer staged according to the International System, using the cervix as the reference organ.

† Five year rates corrected for deaths due to intercurrent disease, per cent (No. at risk).

† Nine cases were found nonresectable at operation, therefore survival rate of cases thought to be clinically resectable is 40 per cent for the 20 cases operated upon.

§ No. of cases (per cent of treated cases).

radical surgical procedures of 73 per cent, appears far superior to those of the radiologic methods. However, when the cases are subcategorized into recurrent and initial stages, it is seen that most of the surgically treated cases had central recurrences after initial Stage I disease, and that the results of retreatment by radium or by roentgen rays are nearly as good for comparable lesions as by surgery. It should be mentioned that 9 cases were found nonresectable and they were excluded in the surgical results. If they were included as surgical failures, the over-all 5 year rate became 40 per cent and that for recurrent Stage I-initial Stage I cases, 63 per cent (7/11).

Incidences of fistulas are about the same in all treatment groups. The radiation treatment groups have the further added complications of chronic proctitis and/or cystitis.

### DISCUSSION

Recurrences of cervical cancer after surgery, after radiotherapy, or after combined forms of treatment differ in time and in manner of presentation. This variation is due to many factors, some of which can be explained.

Firstly, different treatment procedures produce different kinds of alterations in pelvic tissues. Irradiation controls cancer by selective destruction of tumor tissue with sealing-off of avenues of lymphatic spread. Residual injury in normal tissue is usually tolerated. Surgery controls cancer by total ablation of tumor-involved tissue along with an adequate margin of normal tissue and of pathways of spread. The

anatomy of pelvic structures is altered considerably. Thus, cancers recurrent after surgery or after radiotherapy occur in different body environments and are not expected to behave alike. After combined treatments, the situation differs even more. As demonstrated in this study, variations in techniques of radiotherapy can also produce variations in presentation of recurrent cancers, not to mention that this also applies to surgery.

Secondly, the initial population of primary cancer patients in whom the cancer recurs, also differs with treatments. Surgically treated patients are younger and less obese than irradiated ones. They tend to have earlier cancers and a lower incidence of serious concurrent diseases so that more of them are exposed to the risk of recurrences and deaths due to cancer. Differences in host composition between patient populations may produce differences in manifestations of recurrences. Institutions which employ both surgical and radiologic forms of treatment are likely to have two or more very different kinds of patients with recurrent cancers.

Thirdly, the ease of detectability of recurrence differs after surgery and after radiotherapy. Distinction between recurrence and persistence of cervical cancer is difficult in irradiated patients. Healing may sometimes be slow and tumor may be imperceptibly replaced by scar tissue. The presence of local necrosis may further complicate the picture. Pelvic masses may sometimes continue to feel like tumor for long periods before they finally disappear. Graham et al.7 defined recurrence after radiotherapy as regrowth of tumor, either locally in cervix or pelvis, or development of metastasis in patients whose tumor was called healed on 2 examinations I month or more apart or on I examination 6 months or more previously. In this study the 6 month minimum interval of constraint was employed unconditionally in the definition of recurrences in an attempt to produce a better separation between persistent and recurrent cancers.

Diagnosis of recurrence after surgery is easier. Subsequent evidence of tumor in cases whose gross lesion was completely removed and the margins of specimen were histologically free of disease usually means recurrence. Henceforth, there can be at least two kinds of recurrent cervical cancers depending on the type of initial treatment employed, i.e., postsurgical or postradiotherapeutic, and the manner in which patients are selected for initial management of primary cancer at time of diagnosis. The discussion of the results of this study is, therefore, concerned primarily with post-irradiational recurrent cervical cancers.

Incidences reported for recurrent cervical cancers following radiotherapy for primary lesions varied from 15 to 25 per cent.3,5,8 Those for persistent ones were roughly the same, 31 to 32 per cent. The respective incidences of 26.9 per cent in this study are quite close to those reported by Kottmeier.8 Despite the fact that the sample population as well as the physicians who did the examinations differed between institutions, the similarity of incidences of recurrences in 3,376 primary cases in the latter series, as compared to ours in 4,308 such cases is surprising. Although only cases with epidermoid carcinoma were used in this study, the presence of small proportion (less than 5 per cent ) of other histologic types of cervical cancers does not alter the figures appreciably. Selected series of patients with recurrence after mixed treatment methods have also been published:1,2,4,6,11 however, they indicate no figures for incidence of recurrent cancers.

Distribution of cases according to sites of recurrence differed. A 40 per cent incidence of cervical and/or vaginal recurrences in this series is high compared to 30 and 33 per cent in others.<sup>3,8</sup> A 25 per cent pelvic recurrence is somewhat low compared to 43 and 59 per cent, even though the proportion of unknown sites is considered. An incidence of 11 per cent for distant sites is similar to those of others, 11 and 16 per cent.

that the larger field averaged between 14×15 cm. in size, while the smaller field was made as small as possible, approximately 8×10 cm. to cover the remaining preserved tissue induration about the cervix. With this technique, a dose of 3,400 to 4,000 rads was delivered through the larger field, while through the smaller field additional radiation to a total of 6,600 to 7,000 rads was delivered. With this technique the rectum received 6,000 rads, or slightly less, while the bladder received between 5,000 and 6,000 rads. The femoral head dosage now totaled 4,000 rads, while the skin and subcutaneous tissue received between 2,700 and 3,500 rads. Daily and weekly doses totaled 200 rads and 1,000 rads, respectively.

In ovarian carcinoma the pelvic structures were treated to a 4,400-5,000 rad total.

Carcinoma of the bladder was treated by employing a 240° partial rotational technique over the anterior pelvis. This method was described by us. 18 The isodose curves shown in Figure 3 give the dosage distribution resulting from treatment through a 14×15 cm. field when the dosage was calculated to give a total of 6,600 rads at the axis of rotation. This was given in increments of 200 rads a day, 1,000 rads per week, over a 6½ week treatment period. A complete set of isodose curves for 240° rotational therapy was published 18 (Fig. 3).

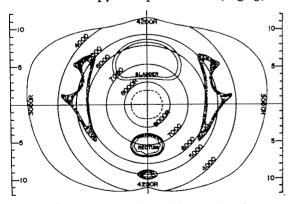


Fig. 1. Isodose curves for  $360^{\circ}$  rotation therapy: 5,000+3,000=8,000 rads tumor dose;  $15\times15$  cm. field to 5,000 rads+ $8\times8$  cm. field to 3,000 rads. R=rads.

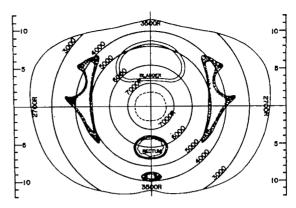


Fig. 2. Isodose curves for 360° rotation therapy: 40,00+3,000=7,000 rads tumor dose; 15×15 cm. field to 4,000 rads+8×8 cm. field to 3,000 rads. R=rads.

### **EVALUATION OF TECHNIQUES**

With the original high dose 8,000 rads technique (Table II), bladder symptoms, chiefly dysuria and frequency, were present in 23 per cent of the patients. No hematuria was noted. In 6 patients (II per cent) bladder complications were produced with this technique; I patient developed a vesicovaginal fistula, while the others developed hemorrhagic dysuria. This type of bladder dysfunction resulted in prolonged disability with periods of recurrence and regression. It persisted for 6 months to 2 years.

Diarrhea was present in 64 per cent of these patients. The diarrhea was moderate to severe but was never hemorrhagic and

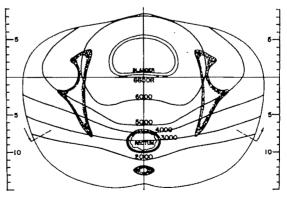


Fig. 3. Isodose curves for 240° rotation therapy: 3,400+3,200=6,600 rads tumor dose; 14×15 cm. field to 6,600 rads at center of rotation. R=rads.

Table II

360° ROTATION THERAPY: NO SURGERY\*

5,000 rads (17×16 cm. field)+3,000 rads (10×12 cm. field)=8,000 rads tumor dose

	Skin	Bone	Bladder	Bowel	Pelvic Fibrosis
Dose (rads)	3,000-4,200	4,8∞	6,000-7,000	7,000	6,000-8,000
Symptoms (per cent)	0	0	23	64	0
Complications (per cent)	0	0	II	15	32

<sup>\* 54</sup> Patients.

did not necessitate cessation of treatment. No skin or bone changes were recorded. However, in long term follow-up of these 54 patients, 5 (9.3 per cent) required colostomies. These were required between 12 and 24 months after the completion of therapy. In 2 patients, colostomies had to be done because of persistence of carcinoma throughout the pelvis and in the abdomen. In 3 patients, colostomies were necessary because of rectal bleeding with rectal narrowing. In I patient a rectovaginal fistula occurred 9 months following therapy. In the other 2 patients complications developed 5 and 9 months following treatment. Three patients (5.5 per cent) had prolonged periods of hemorrhagic diarrhea lasting from 6 to 24 months after the completion of therapy. These were treated medically and the symptoms eventually disappeared. Thus, there was a 15 per cent complication rate involving the rectum and rectosigmoid structures. There were no skin or bone complications or abnormalities in any of these patients.

With the 8,000 rads dosage, parametrial fibrosis was present in 17 patients (32 per cent). This condition developed between 1 and 1½ years following therapy. In no patient, however, did it produce ureteral blockage. Leg edema was seen in 3 patients and this occurred in only one leg. In most patients the fibrosis was an objective finding and was not associated with subjective complaints.

Because the morbidity with the total dose technique of 8,000 rads was far too high, 2 changes were made. First, the field

sizes were reduced and second the dose through the larger field was reduced from 5,000 rads to 3,600-4,000 rads. The small field then received between 3,400 and 4,000 rads. The total dose to the smaller average 10×8 cm. volume now was 7,000 rads, and at the pelvic walls, approximately 5,000 rads (Fig. 2). In this manner both the bladder and rectal doses were reduced by 1,000 rads. We now deliver approximately 5,000 to 6,000 rads to the posterior bladder wall and an average of 6,000 rads to the anterior rectal wall. The skin receives 1,000 rads per week with an over-all treatment period of 7 weeks.

# PELVIC CARCINOMA, MOSTLY CARCINOMA OF THE CERVIX

During the past year we have used a split-dose technique with a 2 to 3 week period of rest at the midpoint of therapy. This method was employed when the patients were unusually sensitive to radiation or were thin and had Stage I and II carcinoma of the cervix, or were very apprehensive. The method was also found to be valuable for patients who had pelvic surgery prior to radiation therapy.

As can be readily seen (Table III) the percentage of symptoms was reduced. Most gratifying was the big drop of major complications. The bladder reactions dropped from II per cent to 3 per cent and the bowel problems from 15 to 4 per cent. Parametrial thickening was decreased by one-half—from 32 to 15 per cent. The fibrosis was less extensive and more pliable, being classified minimal to moderate in degree.

Table III  $360^{\circ}$  rotation therapy: no surgery\* 4,000 rads (14×15 cm. field)+3,000 rads (8×10 cm. field)=7,000 rads tumor dose

	Skin	Bone	Bladder	Bowel	Pelvic Fibrosis
Dose (rads)	2,700-3,500	4,000	5,000-6,000	6,000	5,000-7,000
Symptoms (per cent)	0		28	48	0
Complications (per cent	) 0	0	3	4	15

<sup>\* 100</sup> Patients.

There were no bone, skin or subcutaneous changes recognizable clinically. These are acceptable levels of morbidity. No fatalities were encountered.

The complications that developed among 100 patients treated were:

- One patient had a resection of the terminal ileum for metastatic disease and probably should not be considered a complication.
- 2. One patient required colostomy because of rectal narrowing and bleeding, but no other disease was found.
- 3. One patient had persistent rectal bleeding for more than I year, but was treated successfully by medical means.

The bladder changes were less severe and required medical therapy only. One patient had capillary hemorrhages, and 2 had dysuria of a severe nature for periods of 6 to 20 months. These have all cleared without operation.

We have grouped together all patients who have had any form of abdominal surgery prior to a full-course pelvic radiation therapy. The dangers inherent in this combination have been recognized and documented many times. There were 38 patients in this group; they received 3,600-4,000 rads to the pelvis through a  $14 \times 14$  cm. field in  $3\frac{1}{2}$  to 4 weeks. This was followed by a dose of 3,000-3,400 rads through an average sized field, measuring  $10 \times 8$  cm., during a  $3\frac{1}{2}$  week period. This technique with the tissue dosage is recorded in Table IV.

Although there was no marked increase in symptoms during the treatment period, the severe morbidity following treatment was quite evident. Most of these complications appeared less than I year following completion of therapy and were severe. The average time of onset was between 6 to 12 months following the beginning of treatment.

Five of 38 patients (12.8 per cent) required operations. In 1 a loop of ileum was adherent to the pelvis and required resection; the patient died postoperatively. She had an appendectomy 20 years prior to her cervical carcinoma. Four other patients re-

Table IV  $360^{\circ}$  rotation: radiation therapy after surgery\* 4,000 rads (14×15 cm. field)+3,000 rads (8×10 cm. field)=7,000 rads tumor dose

	Skin	Bone	Bladder	Bowel	Pelvic Fibrosis
Dose (rads)	2,700-3,500	4,000	5,000-6,000	6,000	5,000-7,000
Symptoms (per cent)	0	0	37	34	0
Complications (per cent	:) o	0	7.8	28.2	10

<sup>\* 38</sup> Patients.

quired colostomies because of partial intestinal obstruction, but resection was not necessary.

In 6 other patients (15.4 per cent), persistent rectosigmoid bleeding was present for more than 6 months. No surgery was required.

Parametrial thickening was present in 10 per cent of the patients and was graded as moderate, producing no symptoms or complications.

In no patient was there a clinically evident change in the subcutaneous tissues or bones of the pelvis.

The over-all bowel complication rate of 28.2 per cent is high and demonstrates clearly the dangers of radiotherapy in this group of patients.

### BLADDER CARCINOMA

For comparison with 360° pelvic rotational cobalt 60 teletherapy, a series of 46 patients with bladder carcinoma was studied (Table v). These were all treated through 240° anterior pelvic rotation. A tumor dose of 6,600 rads was administered to the posterior wall of the bladder in 6½ weeks. Nine patients had pretherapy biopsies alone, the remainder had between 1 and 3 operative procedures each. Thirty-three patients had local bladder resections and 5 had been fulgurated 2 to 4 times each.

Only 17 per cent of these patients complained of mild diarrhea during therapy; 28 per cent had mild to moderate dysuria during treatment. The posterior pelvic structures received only one-half of the dose (3,000 rads) that they receive when

360° rotation is used (6,000 rads). The posterior bladder wall received 6,600 rads and the anterior rectosigmoid 3,000 rads. The anterior subcutaneous tissues received 6,000 rads and the pelvic bone area 5,000 rads.

With this technique, there were no bowe complications at all. Persistent dysuria was present in 1 patient and bladder bleeding in another—a 4.3 per cent complication rate.

Moderate pelvic fibrosis was found in 14 per cent of patients, but was not associated with symptoms. There was no subcutaneous fibrosis in the pubic area.

### OVARIAN CARCINOMA

In treating ovarian carcinoma, our program called for a tissue dose of 4,400–5,000 rads to all the pelvic structures. This was initiated through a field averaging 14×14 cm. in size by 360° rotation (Fig. 4) radiation therapy in 5 weeks. At times, in sensitive persons, the dose was divided, so that 3,000 to 3,600 rads were given through the larger field and subsequently 1,400 to 2,000 rads were given through a smaller field. No severe complications were encountered.

### TECHNIQUE COMPARISONS

The chart listing the incidence of major complications with the various techniques described (Table VI), clearly shows that:

 Full-course radiation therapy to the entire pelvis is fraught with danger, when given postoperatively. This applies even when a simple appendectomy precedes radiation therapy.

Table V anterior 240° rotation: bladder carcinoma\*  $3,2\infty$  rads (14×15 cm. field)+3,4 $\infty$  rads (10×12 cm. field)=6,6 $\infty$  rads tumor dose

	Skin	Bone	Bladder	Bowel	Pelvic Fibrosis
Dose (rads)	1,000-6,000	5,000	6,6∞	3,000	3,000-6,000
Symptoms (per cent)	0	0	28	17	0
Complications (per cent)	0	0	4.3	0	15

<sup>\* 46</sup> Patients.

- 2. Rectosigmoid and small bowel injuries are the most likely pelvic structures to be severely affected.
- 3. A pelvic dose of 8,000 rads surpasses the limits of tissue tolerance.
- 4. A similar 360° rotation technique limiting the dosage to the pelvic structures to no more than 7,000 rads is within the acceptable calculable risk range of the bowel.
- 5. With 240° anterior pelvis rotation there are no intestinal complications.
- 6. The bladder complications were high with the 8,000 rads total dosage, but acceptable with the 7,000 rads total dosage. With the 240° anterior rotational method the bladder complication rate also was acceptable.

Table VII lists the dosage levels for the important pelvic structures with a variation of techniques. With this guide many variations of effective treatment can be fitted to meet most specific problems.

### DISCUSSION

Since the sites of pelvic cancer and the location of most of the metastatic lymph nodes are encompassed by the boundaries of the bony pelvis, a technique that supplies curative doses to this volume of tissue is necessary. Of the structures that comprise the pelvis, the rectum and the bowel are the most sensitive; the bladder is less sensitive with our rotational technique. Skin and bone need not be considered. The uterus, ovary and vagina can withstand high dosage of radiation in comparison to the

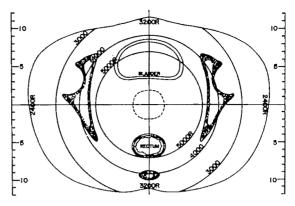


Fig. 4. Isodose curves for 360° rotation therapy: 5,000 rads tumor dose; 15×15 cm. field to 5,000 rads. R=rads.

bowel and the bladder. Thus, dosage levels to the bladder and bowel are critical. Individual tolerance varies widely both within normal cells and tumor cells. Tolerance varies among the specific cells that compose an organ. We found that thin individuals with early disease are apt to be more sensitive. In apprehensive patients, tolerance seems to be decreased. It has been shown by Gros and Block® that as the metabolic rate increases, the danger of tissue injury increases. Nervous patients may have higher metabolic rates during the period of radiation therapy. In contrast, our records reveal better tolerance in calm and confident patients and also in obese individuals. Those with advanced tumor can usually withstand higher doses more safely. When previous abdominal surgery has preceded pelvic irradiation, one can never be certain that bowel loops are not bound in

Table VI

COMPARISON OF COMPLICATIONS WITH VARIOUS ROTATION TECHNIQUES

Technique	Skin (per cent)	Bone (per cent)	Bladder (per cent)	Bowel (per cent)	Pelvic Fibrosis (per cent)
360° Rotation: 7,∞ rads tumor dose Post surgery	0	0	7.8	28.2	Io
360° Rotation: 8,000 rads tumor dose	0	0	11	15	32
360° Rotation: 7,000 rads tumor dose	0	0	3	4	15
240° Anterior Rotation: 6,600 rads tumor dose	o	0	4.3	0	13

Table VII

DOSAGE SCHEMES WITH DOUBLE ROTATION
TECHNIQUE ON PELVIS

	n Rads Tield	Dose in Rads to		
15×15 (cm.)	8×8 (cm.)	Rectum (center)	Bladder (center)	Lateral Pelvic Walls
	3,000	6,000	5,800	5,250
3,500 (7,0		5,800	5,650	5,000
3,∞∞   (7,¢	4,000 000)	5,650	5,450	4,8∞
3,5∞ (6,5		5,5∞	5,350	4,8∞
3,000 (6,5		5,3∞	5,150	4,550

System giving 5,000 rads to rectal center would give about 4,000 rads to lateral pelvic walls.

the pelvis. Such conditions increase the danger of exceeding the tolerance of these sensitive structures.

Rotational cobalt 60 teletherapy alone can be effective and safe in treating pelvic carcinoma without the use of radium or an intravaginal cone. Quimby and Cohen<sup>20</sup> showed the advantages of megavoltage rotational therapy for deep-seated lesions. Brizel, Lanzl, and Duthorn<sup>1</sup> studied many methods of applying pelvic radiation therapy. Both groups stress that rotational therapy delivers the highest dosage to the tumor core area and the lowest dosage to the peripheral structures. This technique delivers a homogeneous dose with no hot (high) or cold (low) dose spots. We have been using this procedure for more than 10 years with good clinical results.14,16

The least damage to the rectum and the posterior pelvis is done with the 240° anterior pelvic rotational technique. The rectal area, however, receives only 3,000 rads. When the disease closely approximates the rectum, it is doubtful that tumor steril-

ization can be achieved with this dose. It might be a good method when the posterior pelvis is clear. A bladder dose of 6,600 rads is appropriate for cancer in the bladder, when this technique is employed. Any combination of 360° and 240° rotational techniques is possible. For instance, an original dose of 4,000 rads to the entire pelvis could be given by a 360° arc and then a 240° rotational arc used to supplement anteriorly or posteriorly. When one suspects undue tissue sensitivity, or in individuals who have had pretherapy surgery, further improvement in the outcome regarding the bladder and rectum may lie in the use of split-dose therapy technique. Recent advocates of split-dose therapy methods are Holsti<sup>11</sup> of Finland, Sambrook<sup>21</sup> of England, and Scanlon<sup>22</sup> and Marcial<sup>17</sup> of the United States. This method is under further investigation in the United States at this time.

Precise, safe levels of radiation therapy vary with the technique. Most published levels of radiation tolerance to the pelvic structures have been reported in dosage plans combining external cobalt 60 irradiation plus radium, or external dosage administered through fixed portals over the pelvis. There have been no reports of tissue tolerance levels with complete rotational therapy techniques. Previous studies on the tolerance of pelvic structures were reported by Kottmeier<sup>16</sup> and Gray and Kottmeier.<sup>8</sup> They indicated a tolerance dose of 4,000 to 4,200 rads to the rectum and a slightly higher one to the bladder, when external orthovoltage and vaginal radium were employed. They reported rectal injuries in 3.9 per cent and bladder injuries in 1.4 per cent of their patients. Ingelman-Sundberg<sup>12</sup> limits pelvic structures to 4,960 rads in 4 weeks and 6,750 rads in 8 weeks using cobalt 60 teletherapy externally through fixed ports with supplemental vaginal radium. He believes that the rectum can tolerate slightly more than 5,000 rads with his method. Graham and Villalba,7 at Roswell Park, found that the pelvic tissue tolerance varies from 3,300 rads to 8,000

1

rads according to specific therapy methods employed. They found that bladder damage occurred in 4 per cent and rectal damage in 3.9 per cent of the patients treated for cervical carcinoma. Studies made by Chau et al.,2 and Fletcher et al.,3 using megavoltage therapy, found no evidence of an absolutely safe level of radiation to the rectum. They contend that 4,000 rads whole pelvis radiation through fixed ports plus vaginal radium is safe. They employ a dose of 6,000rads to the entire pelvis, using fixed ports and 7,000-8,000 rads with advanced pelvic cancer in 8 to 9 weeks. If this is followed by surgery, over 20 per cent of the patients develop severe complications. Frick et al.,4 use 4,000 rads cobalt 60 full course pelvic dose, plus vaginal radium, with fixed pelvic ports and contend that this is a safe technique.

In a fine analysis of pelvic structure tolerance, Garcia<sup>6</sup> states that no critical dose level can be termed lethal, but that a safe and effective zone of dosage exists in most patients. His report showed that high parametrial doses with large fields in treating cervical carcinoma are dangerous, being associated with lower, rather than higher, survival rates in any but advanced pelvic carcinoma. Our dosage levels of safe tolerance, therefore, between 5,000 and 6,000 rads to the bladder and rectum are well within the limits of these publications. This, in association with our complication rate of 3 per cent for the bladder and 4 per cent for the bowel, also coincides with these findings.

### CONCLUSION

1. External rotational therapy for pelvic cancer is by itself sufficient, requiring no radium or other supplemental therapy.

2. A 360° rotation cobalt 60 teletherapy technique, which delivers a tissue dose of 7,000 rads to the rectum and 6,500-7,000 rads to the bladder, is too high and fraught with a high incidence of morbidity.

3. A 360° rotation technique, employing smaller portals and a reduced dosage delivering 6,000 rads to the rectum and 5,500-

6,000 rads to the bladder in 7 weeks, is well tolerated, and is associated with a marked reduction in the frequency of complications.

- 4. In ovarian carcinoma, a tissue dose of 4,500-5,000 rads delivered to the entire pelvis with a 360° rotation technique is well tolerated.
- 5. A tumor dose of 6,600 rads delivered to the bladder and 3,000 rads to the rectum with a 240° anterior arc rotation technique results in minimal bladder complications and a complete absence of rectal complications.
- 6. Rotational radiation therapy of the entire pelvis to a tissue dose of 5,000-7,000 rads, following pelvic or abdominal surgery, is associated with the highest incidence of severe complications.

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## URETERAL STRICTURES AFTER RADIATION THERAPY FOR CARCINOMA OF THE UTERINE CERVIX\*

By JAMES M. SLATER, M.D.,† and GILBERT H. FLETCHER, M.D., HOUSTON, TEXAS

THE incidence of ureteral stricture after radiation therapy for carcinoma of the uterine cervix has been reported to be very low.<sup>1,2</sup> Few publications are dedicated to this subject.<sup>4</sup> There are also few publications reporting on the relief, by irradiation, of obstruction resulting from cancer.<sup>8</sup>

The purpose of this study is to evaluate the status of the ureters in uterine cancer patients treated by irradiation only. Patients having had a lymphadenectomy in addition to radiation therapy are excluded because the surgical procedure is itself fraught with ureteral complications.

### MATERIAL AND METHOD

From September 1954 through June 1966, 1,749 patients with carcinoma of the cervix on intact uterus were treated by irradiation only.

Because of overloading of the diagnostic facilities, 139 patients, usually in the early stage of disease, have not had intravenous pyelography and/or retrograde urography before treatment. In 1,416 patients before irradiation the ureteral status was normal: in 194 patients I or 2 ureters were obstructed, as a rule in patients with Stage III disease and, occasionally, in patients with late Stage II disease.

Almost 90 per cent of the patients were seen on follow-up at the M. D. Anderson Hospital; the remainder were seen at home by their local medical doctor or Public Health or Social Workers. Although routine follow-up intravenous pyelography was not done in all patients, it was usually done

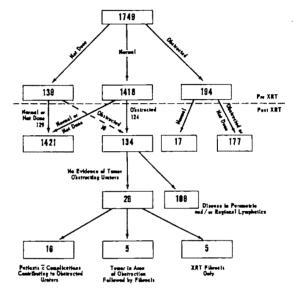


Fig. 1. Flow diagram of ureteral status of patients with carcinoma of the cervix on intact uterus treated at the M. D. Anderson Hospital from September 1954 through June 1966 excluding patients with lymphadenectomy.

in those with late Stage II or Stage III disease and in all patients having the slightest complaint referable to the urinary tract. Therefore, although one cannot be certain that 100 per cent of ureteral strictures have been diagnosed, only a negligible number could have been missed. A few patients with a temporary obstruction secondary to ureteral stones were placed in the group of normal status.

The degree of obstruction is staged as follows:

I. Minimal dilatation of the calyceal system.

<sup>\*</sup> Presented at the Fifty-second Annual Meeting of the American Radium Society, Coronado Island, San Diego, California, March 1-5, 1970.

<sup>1-5, 1970.</sup>From the University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas.

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- 2. Moderate dilatation of the calyceal system.
- 3. Some decrease in function.
- 4. No function.

The ureters involved are coded (right, left), right and left being replaced by 1, 2, 3 or 4 (Table 1). Figure 1 is a flow diagram of the ureteral status.

### RESULTS

Of the 194 patients with obstruction before treatment, 17, or approximately 9 per cent, had relief and remained free of

obstruction through their follow-up period.

From the 1,416 patients with initially normal urograms and the 139 patients without initial urograms, 134 developed ureteral obstruction. The ureteral obstruction resulted from cancer in 108 patients with active disease in the pelvis or along the regional lymphatics.

The 26 patients without evidence of active disease along the ureteral tract are classified into 3 categories:

1. Sixteen patients (Table 1) had surgical procedures after the initial radiation ther-

Table I
OBSTRUCTION WITH CONTRIBUTING FACTORS

Case No.	Stage		Events Preceding Obstruction	IVP
I	IIIA	VV fistula	Ileoconduit	(2, 3)
2	III <sub>B</sub>	V V nstula	Colostomy (sigmoid stricture)	(3, 0)
3	IIB	Postirradiation hysterecto	omy and salpingo-oophorectomy	(0, 2)
4	IIA		Pelvic inflammatory disease	(0, 2)
5	$II_{B}$	Pelvic abscess	Hysterectomy+salpingo-oophorectomy	(1, c)
6	IIIA			(3, 0)
7	$III_{B}$		Purulent peritonitis+colostomy	(2, 3)
8	IB	Bowel perforation or	Multiple fistulae: SB, RV, VV, colostomy	(2, 0)
9	IIIA	fistula to pelvis	Exploratory laparotomy, pre-irradiation (massive pelvic adhesions)	(2, 1)
10	IA	History of pelvic	Cancer vulva with deep groin dissection	(3, 0)
II	IIB	inflammatory disease +pelvic surgery		(0, 2)
12	I <sub>B</sub>	Recurrent tumor	Vaginal wall needle implant Inguinal lymph nodes dissection	(3, 0)
13	IIA	Sansert started Sansert stopped	.38 months postirradiation×6 months .IVP improved	(4, 2)
14	I <sub>B</sub>		RV+VV (no surgery)	(2, 0)
15	III <sub>B</sub>	Fistula	VV (no surgery)	(4, 0)
16	IIA		VV (no surgery)	(2, 4)

RV=rectovaginal; VV=vesicovaginal; SB=small bowel; IVP=intravenous pyelogram.

Table II

FIBROSIS IN AREA OF TUMOR CAUSING OBSTRUCTION

		<del></del>
Case No.	Stage	Progression of Events
17*	III	Bilateral obstruction (4, 2)
18	III <sub>B</sub>	Bilateral obstruction (2, 1)
19*	III	Bilateral obstruction (4, 4)
20	IIIA	Left obstructed (0, 3)
21	III	Left obstructed (0, 3)

<sup>\*</sup> Fixation on one side, extensive but not fixed disease on the other side.

apy for various causes such as pelvic abscess, recurrent tumor or complications necessitating a colostomy or a diversion procedure or complications within the pelvis conducive to fibrosis.

- 2. Five patients (Table II) with Stage III disease developed ureteral obstruction in the area of the parametria and the involved pelvic wall.
- 3. Five patients (Table III) had ureteral obstruction resulting from fibrosis without any apparent contributing factor.

It can be seen from Tables 1, 11, and 111 that, except for 1 patient, at least 1 kidney is functioning well.

Table IV shows the ureteral status as of June 1969. Twenty patients are alive, 13 with morbidity associated with ileoconduit, persistent rectal, or vesicovaginal fistulae,

Table IV

PRESENT STATUS OF THE 26 PATIENTS DEVELOPING
URETERAL OBSTRUCTION POST RADIATION THERAPY

	1	1
Present Status	No. of Patients	Total
Died from complications <2½ years	4	4
Living with morbidity <5 years	5	1.0
Living with morbidity >5 years	8	13
Living and well	I	
Living and well >5 years	3	7
Living and well > 10 years	3	
Died from intercurrent dis- ease or unknown cause	2	2

intermittent symptoms of bowel obstruction, and/or chronic genitourinary tract infection, and 7 without reported complaints. Four patients died from the complications, I patient died from unknown cause and I patient died from intercurrent disease.

### SUMMARY

Ureteral obstruction caused by fibrosis without complicating factors is a rare occurrence.

Table III
OBSTRUCTION WITHOUT CONTRIBUTING FACTORS

Case No.	Stage	Progression of Events	
22	IIA	Bilateral obstruction (3, 3)	
23	IIIA	Right obstructed (2, o) Also rectosigmoid stricture	
24	$II_{\mathbf{B}}$	Right obstructed (2, 0) Also hemorrhagic cystitis	
25	IIA	Right obstructed (4, 0)	
26	$I_{\mathbf{B}}$	Right obstructed (3, 0)	

7

Approximately 10 per cent of the ureteral obstructions resulting from disease are relieved by radiation therapy.

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# VIRULENCE INDICES AND LYMPH NODES IN CANCER OF THE CERVIX\*

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IN A prior report concerned with individualization of treatment for cervix cancer we referred to the critical factors concerned with cure by radiotherapy: (a) radiosensitivity of the tumor; (b) virulence of the tumor; and (c) excellence of treatment. In addition, we offered a protocol based upon our Test Dose Technique, whereby certain patients were chosen for surgery whose lack of response to this small dose of irradiation indicated that radiotherapy would probably fail to cure their disease or might only do so at a level of intensity and radiation injury that was unacceptable by usual clinical standards.

In our analysis of those patients transferred to surgery because of poor response to this test dose of irradiation, we noted that a rate of cure had been attained approximately halfway between those patients with poor Radiation Sensitivity Test (RST) response treated solely by irradiation (net cure rate 32.5 per cent in Stages 1c and 11) and those with good RST response treated with irradiation (net cure rate 72.1 per cent in Stages ic and ii); in this group transferred to surgery because of poor RST response we attained a net cure rate of 56 per cent. This suggested a virulence factor overlapping the radiosensitivity factor that affected the outcome of any treatment and we proposed the parameter of lymphatic invasion by tumor in the original biopsy as a prognostic aid that might afford insight into greater tumor aggression and therefore a requirement for more aggressive radiotherapeutic or surgical treatment or

appropriate combinations of these 2 excellent modalities.

We have enlarged these studies of virulence factors, initiated the study of a host factor and present them now in a preliminary analysis that may contribute to our knowledge of lymph node metastasis and provide some data upon which we may plan appropriate treatment for the more extensive stages of cervix cancer.

# VIRULENCE TUMOR FACTORS AND HOST FACTORS

LYMPHATIC INVASION IN BIOPSY

One can subdivide the problems of radiosensitivity and excellence of radiation treatment in evaluating the cure of cervix cancer by radiotherapy by a consideration of the factors of oxygen tension, protraction, fractionation, intensity and synergistic or adjuvant chemical agents, but there are also qualities in the tumor and its host that modify or even defy the competence of these therapeutic factors.

Without serious invasion of the areas of authority and study of the radiobiologist, one can inspect some histologic properties of the biopsy specimen available to the clinician that can offer information concerning metastasis and survival that may be more significant than most of the radiographic techniques employed including venography, lymphangiography (direct and isotopic), and even pyelography where obstruction is a relatively late event. Since failures of treatment are as often related to unrecognized metastatic disease as to fail-

<sup>\*</sup> Presented at the Fifty-second Annual Meeting of the American Radium Society, Coronado Island, San Diego, California, March 1-5, 1970.

Part of Symposium: The Problems of the Treatment of the Lymph Nodes Metastases from Cancer of the Uterine Cervix. Moderator, James F. Nolan, M.D.

From the Department of Obstetrics and Gynecology, The Mount Sinai School of Medicine and Hospital of the City University of New York, New York.

TABLE I GOOD RST AND BIOPSY LYMPHATICS (Stage I and II Carcinoma of Cervix)

	No. of	L and W	
	Patients	No.	Per Cent
Lymphatics negative	104	90	86
Lymphatics positive	104	42	40

L and W=living and well.

ure to control the local lesion, we must be alert to these clues of the virulence of the fumor.

In a previous analysis of the radiosensitivity of cancer of the cervix11 we noted that failures in those of high sensitivity were related in considerable degree to invasion of lymphatics in the original or control biopsy. We called this simple but apparently significant observation a virulence index to characterize this elusive metastatic quality that some tumors possess. Relevance to survival has been demonstrated for blood vessel invasion in cervix and breast cancer specimens<sup>6,7,19</sup> removed at operation. A similar relationship for lymphatic permeation in surgical specimens to an increased incidence of lymph node involvement and decreased survival has been shown by several Japanese investigators, 17,18

Our studies in irradiated patients were conducted for some years and reported to this Society in 1967. We have extended this group to demonstrate the decreased survival in those patients with lymphatic invasion in the original biopsy who have had a good RST response but who nonetheless developed recurrence or succumbed to their disease following radiotherapeutic treatment. This sign of increased virulence is illustrated in Table 1. To correlate with these survival figures we have also studied our patients treated by radical hysterectomy in Stage 1 and 11, either primarily or due to poor RST response, and once again we can demonstrate a correlation between

TABLE II BIOPSY LYMPHATICS AND LYMPH NODES (Carcinoma of Cervix)

Cervical Lymphatics	No. of Patients	Positive Lymph Nodes	
Lymphacies		No.	Per Cent
Positve	36	16	44
Negative	67	3	4

lymphatic permeation in the original biopsy and an increased incidence of lymph node metastasis (Table 11). These observations are not only important prognostically but could direct our attention toward the requirement for more aggressive treatment in this special group of patients.

#### STROMAL RESPONSE

In our effort to assay the host response of patients with cervix cancer we studied that much neglected zone: the stroma surrounding the tumor. In order to seek clues to the patient's immunologic response to her tumor we counted the round cells in the stroma; i.e., the lymphocytes, plasma cells and monocytes surrounding the tumor cells in the biopsy and in some cases in the surgical specimen. This relatively crude but simple evaluation afforded us some insight into this area, for these preliminary observations indicated an inverse relationship—the presence of stromal response and absence of positive lymph nodes (Table III). To be certain, we must enlarge this

TABLE III STROMAL RESPONSE AND LYMPH NODES (Carcinoma of Cervix)

Lymphocyte Response	phocyte No. of Patients		Positive Lymph Nodes	
Kesponse	Latients	No.	Per Cent	
Good response	36	5	13.8	
Poor response	18	12	66.6	







شر



phase of our study by more sophisticated immunologic methods. Our initial studies indeed tend to support the significance of lymphocytic infiltration as a host tumor restraining factor, as suggested in breast tumors by the work of Black et al., 1 Cutler et al., 4 and Hultborn and Törnberg. 16

### TUMOR DIFFERENTIATION

It is recognized widely that the hazard of sampling error is alway present in grading tumors from a diagnostic biopsy, but we can reduce this error by multiple samples. We must also recognize the accuracy of the pathologists' aphorism that one "makes the diagnosis by the most differentiated area but makes the prognosis by the least differentiated." Many investigators have stressed the importance of clinical staging of cervix cancer for prognosis, dismissing grading as relatively inconsequential. This opinion has been challenged in recent years by the work of Glucksmann, 8,9 Dobbie et al.,5 and Blomfield et al.,2 for they have shown that grading of the tumor does have prognostic significance and can add another dimension to clinical staging in the evaluation of the virulence of a tumor. This relationship has also been demonstrated in breast cancer by Bloom, Haagensen, 4 and in cancer of the endometrium by our own group,12 and others. Our present study of this factor is in accord with this thesis, for we can demonstrate a correlation in our surgical material between lack of tumor differentiation and the presence of involved lymph nodes (Table IV) and some correlation between differentiation and stromal response (Table v).

### DISCUSSION

In our search for biologic factors that can help us choose between the 2 excellent modalities of treatment for carcinoma of the cervix (radiotherapy and radical surgery), we have been guided by the knowledge that these treatments offer an approximately equal cure rate and morbidity rate in the operable stages (Stage I and II) of this disease. Assuredly the empiric method

Table IV

GRADE AND LYMPH NODES

(Carcinoma of Cervix)

Grade	No. of	Positive Lymph Nodes	
·	Patients	No.	Per Cent
Differentiated Grade I	22	0	0
Undifferentiated Grades II and III	31	13	42

of comparing cure rates from various institutions, while offering us models for quality control, can no longer give us substantive leads for individualization and improvement in treatment by increasing cure and diminishing injury. Therefore, we must turn to the analytic approach and utilize the knowledge of biologic factors available clinically or from the increasingly sophisticated laboratory studies of tumor cell kinetics.16 The complexity of some current approaches to tumor cell biology and the gaps in our knowledge about translating them to therapeutic action has persuaded us to rely, for current practice, on the parameters of tumor virulence available to us clinically.

We have demonstrated that a test dose of radiation can help us discriminate between those patients whose tumors will

Table V

GRADE AND STROMAL RESPONSE

(Carcinoma of Cervix)

Grade	No. of	Good Stromal Response	
Grade	Patients	No.	Per Cent
Differentiated Grade I	21	16	76
Undifferentiated Grades II and III	31	16	51

Σ.

TABLE VI
LYMPH NODES AFTER RADIOTHERAPY

Stage	No. of Patients	No. of Patients with +Lymph Nodes
I	28	0
II	23	I
III	4	2

respond readily to an acceptable intensity of radiation and those where unresponsiveness might incur a greater radiotherapeutic debt, suggesting the usefulness of radical surgery in this group. We have suggested now that lymphatic invasion in the biopsy can give us a clue to the aggression of the tumor, the stromal response offers a crude index of the immunologic response of the host and the differentiation of the tumor is a simple assay of the percentage of tumor cells still available for replication. It seems logical to use these parameters for individualization of treatment.\*

Some years ago in an effort to evaluate the efficacy of radiation in destroying cancer in lymph nodes, we subjected a group of patients to retroperitoneal lymphadenectomy at a suitable period after healing of their primary cervical lesion by radiotherapy. This proved disastrous therapeutically because of the high rate of morbidity produced by the cumulative effect of radical surgery on radical irradiation, but it did offer data suggesting that radiotherapy surely had the capacity to destroy cancer in some lymph nodes.10 We have returned to the belief that combinations of surgery and radiotherapy, carefully modulated, may be of value in patients whose indices of virulence suggest the requirement for a greater therapeutic effort than offered in the usual case. We can construct a therapeutic scheme based upon the Clinical Biologic Profile of the tumor derived above:

- 1. Clinical Stage
- 2. Radiosensitivity Test (RST)
- 3. Indices of Virulence
  - a. Lymphatic Penetration in Biopsy
  - b. Stromal Response
  - c. Histologic Grade

By the use of such data, readily attainable clinically, one can make a logical decision for individualization of treatment with the conviction that a greater intensity of treatment is admissible in patients with tumors of high virulence, with the possibility of cure in the face of a higher complication rate where it is clear that more customary treatments will usually fail. One can also take comfort in recognition of factors that allow lesser therapeutic aggression for tumors of lesser virulence where a higher rate of complication is unacceptable.

### CONCLUSION

We propose a therapeutic protocol based upon this clinically obtainable information:

Group A. RST good: virulence indices low. Radiotherapeutic treatment to average intensity

Group B. RST good: virulence indices high. Radiotherapeutic treatment to high intensity including parametrial and paraaortic fields

Group C. RST poor: virulence indices low. Radical hysterectomy

Group D. RST poor: virulence indices high. Radical hysterectomy+postoperative parametrial and paraaortic irradiation.

This therapeutic scheme is designed to avoid penalizing the patient with a tumor

TABLE VII

PROFILE OF VIRULENCE INDICES IN
CARCINOMA OF CERVIX

- 1. Clinical Stage
- 2. Radiosensitivity Test (RST)
- 3. Indices of Virulence in Biopsy
  - a. Lymphatic penetration
  - b. Stromal response
  - c. Histologic grade

<sup>\*</sup> It may be interesting to note that of the 11 patients whose biopsy exhibited all 3 virulence indices, positive lymph nodes were found in 8.

of low virulence by an excess of complications, or those with tumors of high virulence by an excess of recurrence.

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# THE ACCURACY OF LYMPHANGIOGRAPHY IN CARCINOMA OF THE UTERINE CERVIX\*

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THE survival rate of patients with advanced carcinoma of the cervix has increased only slightly despite improved control of tumor in the irradiated area with megavoltage radiotherapy. Patients whose primary tumor is controlled have an increased likelihood of distant spread. At M. D. Anderson Hospital, the survival rate in Stage III, cervical carcinoma has gone only from 41 to 45 per cent and in Stage IIIB from 31 to 36 per cent in the kilovoltage and megavoltage eras respectively. A prime reason for this is the high incidence of lymph nodal metastases in advanced cervical cancer, many of which are outside the 15×15 cm. pelvic portals utilized with the 22 mev. betatron. Improved results with extended radiation fields may be possible with accurate assessment of the extent of disease. This cannot be accomplished by palpation alone.

Roentgenographic assessment has been confined to chest roentgenograms, intravenous pyelograms, and bone surveys. In advanced carcinoma of the cervix, this must be expanded to include lymphangiography and, when needed, venography.

This presentation (1) outlines strict diagnostic criteria for lymphangiographic interpretation of carcinoma and (2) evaluates the accuracy of lymphangiographic diagnosis in advanced cervical carcinoma.

### MATERIAL AND METHOD

All patients (103) with carcinoma of the cervix seen at M. D. Anderson Hospital

from 1961 to 1969 who had lymphangiography as well as biopsy of appropriate lymph nodes are included. Initially no attempt was made to select patients. In the last several years, however, all patients with large bulky lesions, including Stage IIB or greater, were included. All the roentgenographic studies, *i.e.*, lymphangiograms, urograms, chest roentgenograms, arteriograms, and inferior venacavagrams, were evaluated by one of the authors (S.W.) without knowledge of surgical findings.

### DIAGNOSTIC CRITERIA

Interpretation of the lymphangiogram is based on evaluation of a technically adequate examination of both the lymphatic phase (the initial roentgenograms taken at completion of the injection) and the nodal phase (the 24 hour roentgenogram).

The 24 hour roentgenogram allows evaluation of the nodal architecture macroscopically without the presence of lymphatic channels. Frequent nodal and lymphatic abnormalities found in these studies are listed in Tables I and II. The normal lymph node has a granular pattern with an oval or kidney shape. In contrast, abnormal lymph nodes of any etiology frequently are more rounded and may have a definite filling defect caused by tumor deposition, which most frequently causes irregularities along the periphery of the lymph node.

The most reliable criterion for identifying metastasis is the presence of a nodal defect not traversed by lymphatics. This

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### TABLE I CRITERIA-ABNORMAL LYMPHANGIOGRAM LYMPHATIC PHASE

- I. Filling defect in a node not traversed by lymphatics
- 2. Lymphatic obstruction and/or distortion

3. Collateral

Lymphatic—lymphatic -Lymphatic-venous circulation € Lymphatic-prelymphatic

- 4. Lack of normal number of lymphatics on initial examination
- 5. Stasis of contrast medium in lymphatics on 24 hour examination

requires scrutiny of lymphatic and nodal phases in multiple roentgenographic projections. Although this phenomenon is seen in other diseases with localized destruction in a node (e.g., abscess or caseation necrosis), in a patient with carcinoma of the cervix, metastasis must be the primary consideration.

When the lymph node is replaced completely by metastatic disease, there is no nodal opacification. Total nodal replacement can be inferred if there is associated obstruction or distortion of the normal lymphatic pathways. There are normally 3 major iliac lymphatic trunks in the pelvis which are more or less parallel and lie along the major iliac vessels. The presence of less than 3 lymphatic pathways or complete obstruction in a technically adequate study are secondary evidence of metastasis (Table III). This secondary evidence should be confirmed by other studies such as venography, intravenous pyelography, or possibly arteriography. When venography demonstrates an impression of a mass on

### TABLE II CRITERIA-ABNORMAL LYMPHANGIOGRAM NODAL PHASE

- 2. Complete replacement
- 3. Rounded lymph node

the vein in the area of lymphatic obstruction, one may be fairly certain that this represents metastatic disease. Obstruction of the inferior vena cava by externally placing a balloon or other compression device at its bifurcation results in maximum dilatation of the external iliac veins and opacification of the internal iliac veins.2 This provides additional information about the internal iliac lymph nodes, which are not uniformly filled by lower extremity lymphangiography.

Lymphatic obstruction may or may not be associated with collateral circulation. Lymphatic to lymphatic collaterals lead to the opacification of channels ordinarily not visualized. This must be differentiated from such anomalous channels as the circumflex iliac. Prelymphatic or paralymphatic pathways include the interstitial, perivascular, and perineural spaces; the body's potential cavities (pleural, pericardial, and peritoneal); and all those pathways which transport lymph from the cell via nonendothelial-lined channels to the well defined endothelial-lined lymphatics. Retrograde flow into these avenues is a manifestation of lymphatic obstruction and collateral circulation. Another alternate pathway, lymphaticovenous anastomosis, the direct communication between a lymphatic vessel and vein, is utilized primarily when there is lymphatic obstruction.

Lymphatic obstruction may be the result of pelvic or retroperitoneal fibrosis or of surgical intervention. In the absence of these factors, lymphatic obstruction is most frequently caused by metastatic disease.

### TABLE III EVIDENCE OF METASTASIS

### Definite Evidence of Metastasis

1. Nodal defect not traversed by lymphatics

### Secondary Evidence of Metastasis

- 1. Total replacement of lymph nodes
- 2. Lymphatic obstruction with or without collateral circulation

<sup>1.</sup> Filling defect (partial replacement) crescent deformity

Stasis of contrast material in the lymphatics found at the 24 hour examination often is caused by lymphatic obstruction. This finding may be present without obvious interruption of the normal pathways and may be attributed to an increased central venous pressure as in congestive failure or constrictive pericarditis. Most frequently, local stasis is unexplained and may be the result of a chemical lymphangitis.

We therefore give the following interpretations of our findings on lymphangiograms: positive—unequivocal evidence of disease; suspicious—requires further evaluation, especially by venography; or negative—no evidence of macroscopic disease in the visualized lymph nodes. Only the positive diagnosis is of any significant clinical use.

#### RESULTS

Of the 103 cases in this study, 41 were diagnosed as positive for metastatic disease, later confirmed by biopsy. As shown in Table IV, only I lymphangiogram was diagnosed as positive with the subsequent biopsy proving negative. Forty-nine were negative on both roentgenographic evaluation and histologic study. Another 12 had negative interpretation on lymphangiography but proved to be positive on biopsy. When a definite positive diagnosis was made, the accuracy was 97.6 per cent (41 of 42). Therefore, on a roentgenographic basis only, at least 40 per cent of the group (41 of 103) had definitely positive lymph node disease that could not be de-

TABLE IV

CORRELATION OF LYMPHANGIOGRAMS
AND BIOPSIES

Lymphangiogram	Biopsy	No.
Positive	Positive	41
Positive	Negative	ľ
Negative	Negative	49
Negative	Positive	12
Total		103

TABLE V
POSITIVE BIOPSIES

Lymphangiogram and biopsy positive Lymphangiogram negative—biopsy positive				
	_			
Total positive biopsies	53			

duced from palpatory findings. As seen in Table v, of the 53 patients with positive biopsy specimens, we were able to diagnose 41 (77.7 per cent) by lymphangiography.

Table vI lists the groups of lymph nodes biopsied. In the group with positive roent-genographic and biopsy evidence of malignancy, there were 14 with positive aortic lymph nodes and 10 with disease in the common iliac area. Most of these were beyond the usual field of pelvic irradiation for cervical carcinoma.

Only I patient in this series had had a pelvic lymph node biopsy prior to the lymphangiography. However, 34 women had had previous pelvic irradiation (Table VII). It is stressed that, even in the 15 patients with previous irradiation who had both roentgenographic and histologic proof of recurrence, previous irradiation did not invalidate the interpretation of the subsequent lymphangiogram.

Eight patients were excluded from the study because the abnormal lymph node seen on lymphangiography was still present

TABLE VI
GROUPS OF LYMPH NODES BIOPSIED\*

Lymph Node Group	Pos.‡- Pos.†§	Neg.‡- Neg.§	Neg. §- Pos.†§
Aortic	14	69	6
Common iliac	10	4.I	0
External iliac	20	45	7
Internal iliac	I	37	Ö
Obturator	0	36	3
Inguinal	2	ō	ŏ
Supraclavicular	I	0	0

<sup>\*</sup> Does not include actual numbers of lymph nodes, only groups.

Biopay diagnosis.

<sup>†</sup> Does not include negative lymph nodes removed at the same time.

<sup>‡</sup> Lymphangiogram diagnosis.

on follow-up roentgenograms obtained shortly after surgical exploration. This emphasizes the value of careful monitoring of the lymph node biopsy by roentgenography during the operation.

### DISCUSSION

The place of lymphangiography as a diagnostic method in evaluating cancer patients has never been fully established. We believe that this is mainly the result of two factors: (1) strict criteria are not followed in making a definite diagnosis of metastatic disease; and (2) physicians are discouraged by so-called false negative studies. Our experience of diagnosing 41

TABLE VII
PREVIOUS IRRADIATION

Pos.*–Pos.†	$Neg.*-Neg.\dagger$	Neg.*-Pos.	
15	14		
Previou	us Lymph Nodal	Biopsy	
0	I	0	

<sup>\*</sup> Lymphangiogram diagnosis.

of 42 (97.6 per cent) as definitely positive for metastatic disease, which was confirmed by biopsy of the exact group of lymph nodes, was made possible by follow-

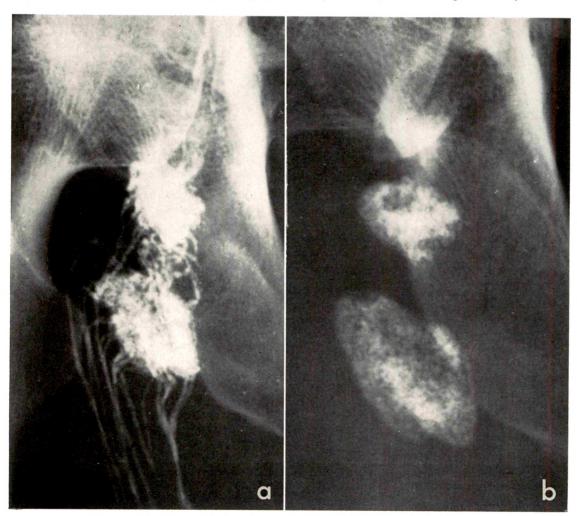


Fig. 1. (a) Normal lymphatic phase with afferent channels entering at the periphery and efferent channels leaving at the hilum. (b) Normal nodal phase.

<sup>†</sup> Biopsy diagnosis.



FIG. 2. Absence of I of the 3 lymphatic channels with filling defects in the external iliac lymph nodes, which are not traversed by lymphatics.

ing the strict criteria previously outlined.

The second objection, *i.e.*, false negatives, supports our contention that only a diagnosis of definitely positive disease is of any clinical use. This is because metastases less than 3 mm. in diameter will not cause a significant defect in the lymph node to be detectable by roentgenographic examination. Moreover, all pelvic and aortic lymph nodes are not filled by the contrast material. These two facts readily explain why a roentgenogram could be called negative and a subsequent biopsy be positive.

Figure 1, a and b, illustrates the normal architecture of a lymph node with its afferent and efferent lymphatics. In contrast, Figure 2 shows only 2 of the normal lymphatic channels with a filling defect in the distant lymph nodes. In addition, no lymphatics traverse these nodes. However, we do not always have such con-

clusive evidence of metastasis. In Figure 3, we see lymphatic obstruction in the region of the left common iliac area. The subsequent inferior venacavagram (Fig. 4) shows a defect in the left common iliac vein in the region of the lymphatic obstruction. These two findings allow us to make a definite diagnosis of metastatic disease based on secondary evidence.

Previous pelvic irradiation does not distort the lymphatic channels or the nodal architecture; therefore, subsequent lymphangiographic interpretation is still accurate.

The fact that there were 14 patients with both positive roentgenographic and biopsy evidence of aortic disease in addition to 10 patients with similar findings in the common iliac areas supports the usefulness of lymphangiography, because with conventional pelvic irradiation for carcinoma of



Fig. 3. Complete lymphatic obstruction at the level of the left common iliac vessels.

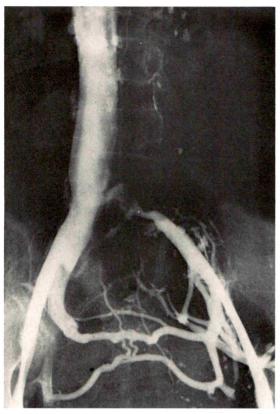


Fig. 4. Inferior venacavagraphy demonstrating defect in left common iliac vein. Same patient as in Figure 3.

the cervix these lymph node areas would have been beyond the irradiation fields. We now are employing extended fields when a definite diagnosis of metastatic disease is made. Irradiation fields are extended to the top of L-4 when positive external iliac lymph nodes are seen and to T-12 when positive common iliac or aortic lymph nodes are diagnosed. Conclusions about extended field irradiation cannot yet be assessed.

### CONCLUSIONS

- I. Adherence to strict diagnostic criteria results in a high degree of accuracy in positive lymphangiograms.
- 2. Negative lymphangiograms are not useful clinically.
- 3. Inferior venacavagraphy may assist in evaluation of lymphatic obstruction.

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# THE VALUE OF PELVIC VENOGRAPHY AND LYMPHOGRAPHY IN THE CLINICAL STAGING OF CARCINOMA OF THE UTERINE CERVIX

### ANALYSIS OF 105 PROVEN CASES BY SURGERY

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IN A significant number of patients with clinically early cancer of the uterine cervix, regional lymphatic metastases may be present but undetected by the usual diagnostic methods.<sup>8,5,11,12,29</sup> In an attempt to improve the accuracy of clinical staging of carcinoma of the uterine cervix and to aid in the management of such patients, a study of combined lymphography and pelvic venography was undertaken.

### MATERIAL

Lymphography and pelvic venography were performed on over 300 patients with pelvic malignancy from 1962 to 1968 at 3 Medical Centers: Thomas Jefferson University Hospital; Yonsei University Severance Medical Center; and Jersey City Medical Center, New Jersey College of Medicine. Of this group, 175 patients had cancer of the uterine cervix and were selected for this evaluation. The age range of the patients of this series was from 26 to 72 years.

Since this study was to detect early extension of the neoplasm, in the majority of the patients selected the carcinoma was in Stages I and II as defined by the International Classification. Twenty-one cases of advanced carcinoma were also included in order to establish typical findings for venographic and lymphographic

involvement. Cases of carcinoma in situ or fundal adenocarcinoma are excluded from this report.

Lymphography was performed in 145 patients. One hundred and five patients were operated on with 12 deaths occurring within a period of several months following surgery. Of the latter patients autopsies were performed on 7. Several of these deaths were due to complications of surgery and several to unsuspected distant metastases.

Five patients were treated with chemotherapy and 51 with irradiation (Table 1). It is not our purpose to present the results of therapy at this time.

### TECHNIQUE

Initially, lymphography was performed prior to venography but superimposition of opacified lymphatics and lymph nodes was found to be confusing in detailed analysis of the pelvic veins (Fig. 1). Hence, the venography was performed first in this sequence of studies. Two different approaches to venography have been studied: (1) bilateral femoral vein injection with external inferior vena cava compression; and (2) intraosseous injection of contrast medium. The intraosseous method results in somewhat better visualization of the venous plexus of the uterus, bladder

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ANALYSIS	ΟF	175	PATIENTS	WITH	CARCINOMA	OF	THE	CERVIX

Stage No.	Venogram	Lymphogram	Therapy (primary)			
Stage	110.	Urogram	Cavagram II.:1-t1	Surgery	Irradiation	Chemotherapy
I	86	86	64 (1)	65	13	0
HA HB	47 21	47 21	4 <sup>2</sup> 20	28 8	17 12	0
Ш	12	12	12 (1)	4	8	0
IV	9	9	7	0	I	5
	175	175	145 (2)	105	5 I	5

and about the sacrum. However, because of the high patient discomfort, frequent necessity for general anesthesia and greater complexity of the procedure, this method has been limited to obese patients in whom adequate external vena caval compression cannot be obtained.

Because of some variations in technique which we feel are quite significant, a brief description of each method is presented.

### FEMORAL VEIN VENOGRAPHY

As with arteriographic procedures, we have found premedication with meperidine 50 to 100 mg., nembutal 100 mg., and benadryl 50 mg. an excellent and frequently necessary sedation for patient comfort.

A number of patients have been studied with teflon catheters of O.D. 0.095 inches and I.D. of 0.085 inches placed in each femoral vein using the Seldinger technique. More recently a disposable Longdwell 18 gauge teflon catheter needle (Fig. 2A) has been introduced into each femoral vein and advanced about 10 cm. above the puncture site. In this way, the tip usually will be found to lie near the junction of the external iliac and hypogastric veins. A compression belt utilizing an inflatable rubber bladder or balsa wood block is placed slightly to the right of the umbilicus and tightened enough to compress the vena

cava (Fig. 2*B*). A little practice is necessary to find the correct amount of pressure which is usually just below that which produces patient discomfort.

Thirty cc. of warmed contrast medium,



Fig. 1. Femoral venography performed after bilateral lymphography. The anatomic details of the iliac veins and the inferior vena cava are obscured by the superimposed iliac and paraaortic lymph nodes.

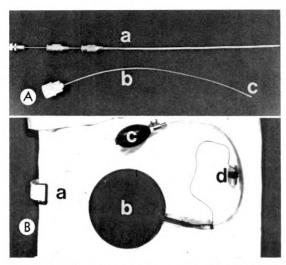


FIG. 2. (A) A catheter needle (modified Rochester or Longdwell) 18 gauge, 6 inches. A plastic stylet (b) is fitted into the plastic catheter (a) following the puncture of the femoral vein. The catheter with stylet is gently advanced about 10 cm. so that the tip of the catheter is placed in the external iliac vein near the union with the hypogastric vein. The smooth surface and blunt tip of the plastic stylet (c) prevents accidental perforation of the venous wall while advancing the catheter. (B) Abdominal compression device, consisting of a compression band (a), a rubber balloon (b), a pump (c), and a pull-string (d).

meglumine diatrizoate 60 per cent, is injected through each cannula in 2 seconds. Serial roentgenograms are obtained at 2 per second for 2 seconds. At this time the compression is quickly released and additional roentgenograms of 1 per second for 4 seconds are obtained.

The abdominal compression, properly done, allows filling of the hypogastric, lateral sacral, uterine and vesical veins<sup>6,10</sup> (Fig. 3,  $\mathcal{A}$  and  $\mathcal{B}$ ). Following release of the compression, the common iliac veins and the inferior vena cava will be outlined.

#### INTRAOSSEOUS VENOGRAPHY

The pelvic veins can be outlined by intraosseous injection of contrast medium into the pubic bones, ischial tuberosities, iliac crests or the greater trochanters of the femurs.<sup>17,20,25,30</sup> In our experience the injections into the greater trochanters have been most consistently useful. The procedure can be performed employing the previously described sedation and good local infiltration of the periosteum, but many patients will still have considerable discomfort; hence, one usually has to resort to general anesthesia. With the patient supine, the feet are placed in internal rotation and maintained with tape. A 16 gauge bone biopsy or aspiration needle is introduced into each greater trochanter, usually with the aid of light tapes with a small hammer. Again 25 to 30 cc. of the warmed meglumine diatrizoate 60 per cent solution is injected through each needle in about 5-10 seconds. Filming is begun near the end of the injection and is made at a rate of I per second for 5 seconds and I every 3 seconds for 3 more exposures.

At the end of each procedure, several abdominal roentgenograms are obtained to visualize the urinary tract.

#### LYMPHOGRAPHY

A day or more following the pelvic venoggraphy, lymphography was performed on 145 patients. In 2 of the 145 patients studied, it was possible to cannulate only one lower extremity. Lymphography resulted in visualization of the lymphatics and lymph nodes in only one iliac area, but in fairly good demonstration of the lymphatics in the sacral lymph node region and the lower paraaortic groups.

The technique of lymphography is essentially as described in the literature. 15,16,28 The lymphatic channels in each foot are visualized with patent blue violet. Under local anesthesia they are cannulated and 8–10 cc. of ethiodol is injected over about a 60–90 minute period. Roentgenograms are obtained at the conclusion of injection, in 24 hours and in 1 month. A stretcher especially designed to obtain roentgenograms of the extremities, pelvis, abdomen, and chest with minimal change in patient position has been very helpful. 16

In addition to anteroposterior, lateral, and oblique roentgenograms of the pelvis and abdomen, a roentgenogram with 45° cephalad angulation of the roentgen tube

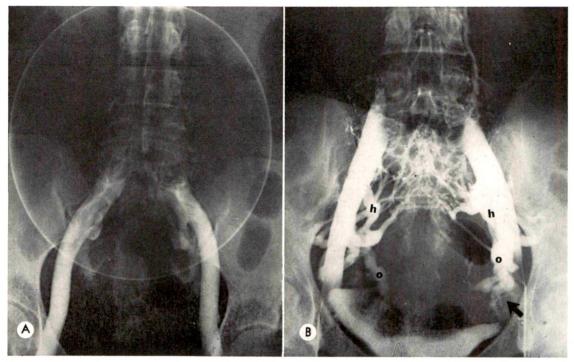


Fig. 3. (A) The compression band is wraped around the patient's waist at the level of the umbilicus. The balloon is then placed under the compression band slightly lateral to the umbilicus towards the right and the side belts are fastened. The balloon is inflated until the pressure reaches slightly below the systolic pressure. There is retrograde filling of the hypogastric and presacral venous plexus. The external and common iliac veins are smooth without deformity. Normal pelvic venogram. (B) A 52 year old patient with Stage 1 carcinoma of the cervix. In retrospect the left hypogastric (h) and obturator veins (o) appear to be slightly displaced laterally with an equivocal indentation (arrow). The venogram was initially considered to be within normal limits. At operation, there were a few metastatic lymph nodes in the obturator fossa.

with the central ray passing through the projections will be separated clearly with sacrum has added much information. Many lymph nodes superimposed in the other

this angulation (Fig. 5B). If uncertainty still exists about one or more lymph nodes.

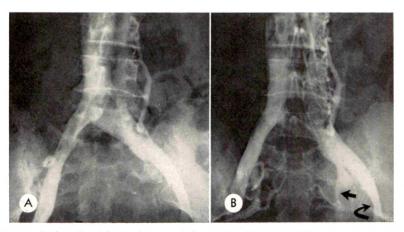


Fig. 4. (A) A 38 year old female with carcinoma of the cervix, Stage IIB. The venogram without compression shows no definite evidence of mass lesion. (B) The compression venogram, however, shows indentations of the hypogastric and external iliac veins due to lymph node metastases (straight and curved arrows).

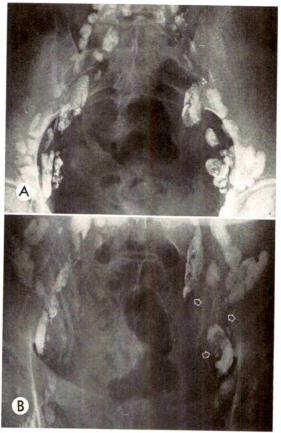


Fig. 5. (A) A 34 year old female with carcinoma of the cervix, Stage 1. Anteroposterior and oblique views were considered to be within normal limits. (B) The "inlet view" of the pelvis, however, clearly demonstrates irregular filling defects in the external iliac lymph nodes (arrows) on the left side.

tomograms (Fig. 6, *inset*) are of great value in obtaining more detailed morphology of the questionable lymph nodes.<sup>9,23</sup>

#### RESULTS AND DISCUSSION

Operations were performed on 105 of the patients studied. Of this group, 24 were found to have pelvic metastatic disease. The use of pelvic venography to detect such disease has been reported by others, 6,10,17,30 but its employment in combination with lymphography has not been extensively documented. 2,18,20

The changes of metastatic disease reflected in the pelvic venograms of these 24 patients are summarized as follows:

(1) Complete obstruction of the major veins, external iliac, or inferior vena cava, with extensive collateral circulation was observed in 4 patients (Fig. 6, A and B; and 7).

- (2) Partial obstruction of the major veins with collateral channels was seen in 5 patients (Fig. 8).
- (3) Indentation or displacement of the major veins without demonstrable collateral was seen in 6 patients (Fig. 9).
- (4) Indentation or displacement of smaller veins without collateral channels was demonstrated in 5 patients (Fig. 4, A and B).
- (5) Probable normal venogram was noted in 3 patients. In retrospect, 1 of them is abnormal (Fig. 3B).
- (6) A normal venogram was seen in 3 cases (Fig. 3A).
- (7) A combination of 2 or more of the above findings was noted in 6 cases.

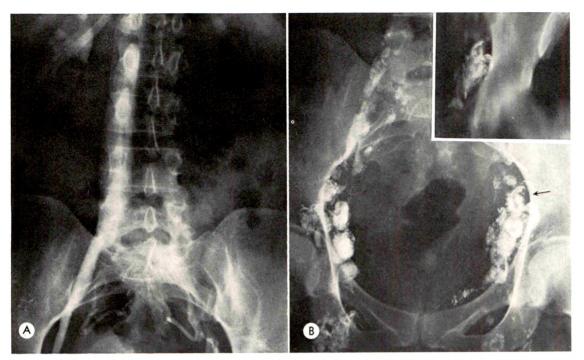


Fig. 6. (A) A 38 year old patient with carcinoma of the cervix, Stage IIA. Complete neoplastic occlusion of the common iliac vein and proximal portion of the external iliac vein on the left side. (B) The lymphogram shows equivocal filling defects in the external iliac lymph nodes (arrow). (Inset) The tomogram, however, clearly demonstrates irregular marginal defects of the lymph nodes, typical of metastases.

The intravenous urograms of these 24 patients showed nonfunction of one kidney in 3 instances and varying degrees of hydronephrosis in 7 patients: marked in 2, moderate in 3, and slight in 2.

The lymphographic findings in these 24 patients with metastatic disease are as follows:

(1) Lymphatics: In 14 patients, varying degrees of lymphatic obstruction were manifested by dilatation of the afferent lymphatic channels, stasis, extravasation, and reflux of contrast medium into the collateral channels in the vicin-



Fig. 7. A 44 year old female with Stage I lesion. The left common iliac vein is completely obstructed and there is an indentation of the external iliac vein. Note the collateral circulation developed via the iliolumbar vein, lumbar vertebral plexus, and presacral venous plexus.

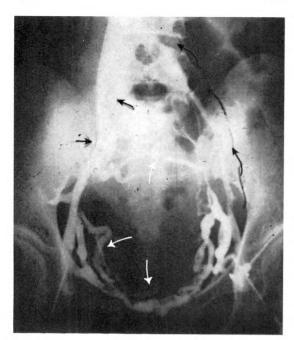


Fig. 8. A 42 year old patient with Stage IIA lesion. There is a diffuse narrowing of the left external and common iliac veins (curved black arrows) with collaterals via obturator and pubic veins as well as the vesical and presacral plexuses (white arrows). Slight indentations are also seen in the right common iliac vein (straight black arrows).

ity of the involved lymph nodes (Fig. 10A; and 11A).

(2) Lymph Nodes: Enlarged lymph node filling defects were demonstrated in 10 patients (Fig. 10B; and 11B). Enlarged lymph nodes without demonstrable filling defects were noted in 1 instance. Normal sized lymph nodes with equivocal filling defect were seen in 2 cases, whereas 5 other lymphograms were within normal limits.

The reported lymphographic accuracy of metastatic lymph nodes in gynecologic carcinoma varies considerably; depending on the authors, its range is from 65 to 92 per cent.<sup>1,2,8,24,26,27</sup> In our opinion, the rate of accuracy in the diagnosis of lymph node metastases is closely related to the clinical stage of the lesion.

The comparative diagnostic accuracy between venography and lymphography is shown in Table II. The diagnostic yields of pelvic venography in Stage I are significantly higher than those of lymphography, the ratio being 8 to 5. In Stage II, an equal number of positive findings were demonstrated, whereas a higher incidence of positive lymphograms was seen in Stage III.

The venograms of 19 patients and the lymphograms of 17 patients in this group of 24 were found to have histologic proof of metastatic disease. In the analysis of the roentgenograms, 2 of the venograms were falsely interpreted as indicating metastatic disease. Each showed displacement of a major vein. In 1 instance, this was found to be due to a tortuous iliac artery and in the other due to large inflammatory lymph nodes.

Similarly, the lymphograms of 2 patients were falsely interpreted as representing metastatic disease. The abnormal lymph nodes in 1 patient were due to inflammatory hyperplasia (Fig. 12, A and B) and in the other to focal fibrosis.

In these 24 patients, the pelvic venograms of 4 and the lymphograms of 5 were felt to be negative for the presence of metastatic disease. An interpretation on

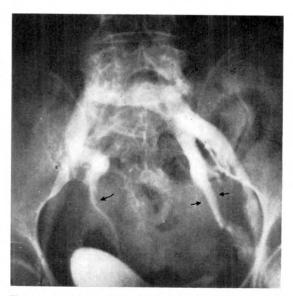


Fig. 9. A 52 year old patient with Stage IIB lesion. Multiple segmental narrowings are seen in the external and common iliac veins bilaterally due to diffuse lateral extension of the disease (arrows). No collateral channels are demonstrated.

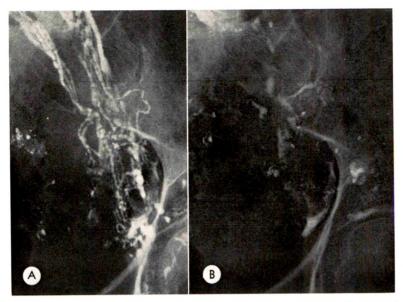


Fig. 10. (A) A 59 year old patient with Stage IIB lesion. The afferent lymphatic channels are irregularly dilated with several collateral channels. (B) The 24 hour lymphogram shows enlarged matted iliac lymph nodes with extensive filling defects due to metastases.

one of these venograms was made in spite of poor filling of the hypogastric veins and was felt to be normal. The authors would now not render an opinion on the basis of such unsatisfactory roentgenograms.

Of the 5 patients with normal lymphograms, I was a unilateral study in which only one side of the pelvis was filled with contrast material. It happened that there were lymph node groups on the contralateral side which contained metastatic disease. One of the areas of deficiency with present lymphographic techniques is that

the medially placed pelvic lymph nodes, which are usually the first involved in metastatic disease from the cervix, generally are not outlined. The other major group of lymph nodes usually involved with metastatic disease, the hypogastric group, is also difficult to fill by lymphography, but the area is well demonstrated by pelvic venography<sup>13,14,21</sup> (Fig. 13, A-C).

In a few instances in the urographic study, pressure on the bladder or ureteral compression and/or displacement may be the only indication of metastatic deposits.

Table II

COMPARATIVE DIAGNOSTIC ACCURACY

Venography vs. Lymphography

(24 proven metastases in 105 operated cases)

Stage	Proved Metastases	Positive Venogram Positive Lymphogram	Positive Lymphogram Negative Venogram	Positive Venogram Negative Lymphogram	V/L ratio
I	IO	4	I	4	8/5
II	10	7	I	I	8/8
III	4	3	1	0	3/4
	24	15	3	5	19/1

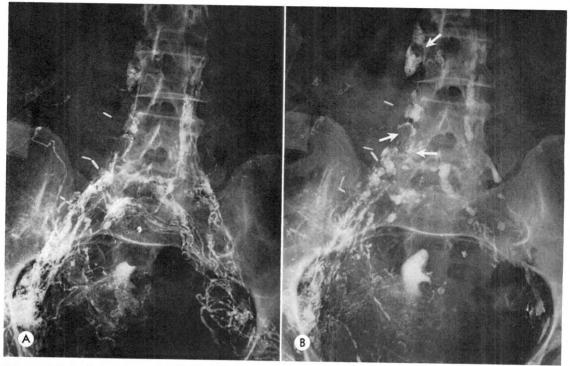


Fig. 11. (A) A 48 year old patient with Stage IIIE lesion. The initial lymphogram, taken at the completion of injection, reveals multiple lymphatic obstructions manifested by numerous collateral channels with stasis, visceral backflow, and extravasation of opaque medium. A pelvic lymphocyst is seen from previous surgery. (B) The 24 hour lymphogram shows multiple filling defects involving the iliac and paraaortic lymph nodes (arrows). At laparotomy, diffuse metastasis was seen involving the right ureter, inferior vena cava, and psoas muscle.



Fig. 12. (A) A 55 year old patient with carcinoma of the cervix, Stage IIA. Scalloping is noted in the inferior vena cava (white arrows) associated with irregular narrowing of the external iliac vein on the right side (black arrows) thought to be due to lymph node metastases. (B) The lymphogram shows foamy or lacy appearance of the common iliac and paraaortic lymph nodes, suggestive of lymphoma or a typical metastasis. The histologic diagnosis was that of lymphatic hyperplasia due to infection.

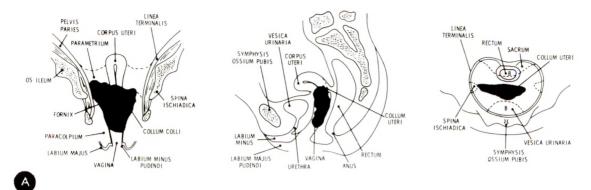


Fig. 13. (A) A 45 year old female with Stage IIB lesion. A chart of the clinical examination revealed the right parametrium to be almost completely obliterated, but no nodular surface was palpable. The lesion extends downward to involve the upper half of the vagina with partial involvement of the left parametrium.

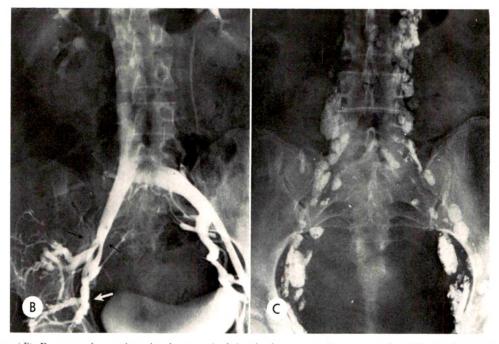


Fig. 13. (B) Because the patient is obese and abdominal compression extremely difficult, bilateral intraosseous venography was performed via the greater trochanters. The obturator and hypogastric veins are displaced laterally (black arrows) with irregular narrowing of the external iliac vein on the right side (white arrow). An indentation is noted in the lateral aspect of the hypogastric vein on the same side. The findings indicate metastatic involvement of the hypogastric and external iliac regions. (C) The 24 hour lymphogram shows no distinct abnormality, although equivocal obstruction of the lymphatic channels was noted on the initial lymphogram.

A nonfunctioning kidney was noted in 3 advanced cases. The prognostic significance of abnormal urograms in the patients with carcinoma of the uterine cervix has formerly been established.<sup>4,22</sup> The use of pelvic venography, lymphography and urography

in all patients with pelvic cancer, therefore, is complementary.

The incidence of metastatic disease in this group of patients was found to be 15.4 per cent in Stage I and 27.8 per cent in Stage II. These percentages agree with

TABLE III

RADIOLOGIC-PATHOLOGIC CORRELATION

OF LYMPH NODE METASTASES

Stage	No.	Radiologic (VG, LG, IVU)	Histologic Metastases	Per Cent Accuracy
I	65	8	10	
IIA	65 28	4\9	5)10	
IIB	8	5)	5) 10 5)	
III	4	4	4	
	105	21	24	87.5

VG=venogram; LG=lymphogram; IVU=intravenous urogram.

large numbers of published data on the incidence of metastatic lesions in the various stages of cancer of the uterine cervix. 3,5,11,12 Claiborne et al.5 in 1960 collected cases from 8 authors and reported incidences of regional lymph node metastases of 16.6 per cent in 857 patients with Stage 1 and 32.2 per cent in 832 patients with Stage 11 carcinoma of the cervix. Similar incidences of lymph node metastases in Stage 1 and 11 disease of 17.2 per cent and 32.9 per cent, respectively, were found by Navratil-Graz who in 1955 reviewed 1,642 cases from 9 authors. 19

The distribution of lymph node metastases from carcinoma of the cervix has been well documented.<sup>8,11,12</sup> The obturator or middle group of lymph nodes in the internal iliac chain usually is the first group affected.<sup>13</sup> In successive incidence, the external iliac,

hypogastric, parametrial, paracervical, and common iliac lymph nodes generally are involved. This involvement lends itself fairly well to the methods of examination reported in this study. Thus, using such combined methods in this small series of patients with cancer of the cervix, the incidence of detection of metastatic disease was 80 per cent in Stage II, 90 per cent in Stage III, and IOO per cent in Stage IV.

Our present inability to specifically outline other lymph node groups by lymphography will preclude finding metastatic lesions in patients in whom the other lymph node groups are invaded initially. 14.21,24 As indicated by the increase to 100 per cent abnormality in both venograms and lymphograms when the neoplasms are more advanced, the detection of the extensions will be clearly demonstrated by these studies.

Of the 175 patients in this group, adequate follow-up could be obtained only in 126. As shown in Table IV, the prognosis of the patients with abnormal venograms was poor. The 8 patients with complete occlusion of the major pelvic veins all died within 18 months. This is not unexpected as an abnormal venogram is a manifestation of spread of disease even though patients on initial examination appear to be in clinical Stage I or II.

It is hoped that the increased use of these combined procedures may make selection of treatment methods of patients with carcinoma of the cervix more specific and will result in improved therapeutic results.<sup>7</sup>

Table IV

PROGNOSTIC SIGNIFICANCE OF VENOGRAMS
(1962–1965)

Stage	Negative	3 Yr. Survival		Positive	3 Yr. Survival	
Stage	Venogram	No.	Per Cent	Venogram	No.	Per Cent
I II III IV	54 39 2 0	47 25 1		6 11 6 8	3 4 1	
	95	73	76.9	31	8	25.8

#### SUMMARY

- 1. A somewhat different technique of pelvic venography with the use of a commercially available teflon needle and a compression device is described. Some indications of the intraosseous method are discussed.
- 2. The anatomic detail of the veins may be superimposed by lymph nodes, if lymphography precedes venography; hence, venography is more useful as the initial study.
- 3. Pelvic venography may provide more information as to the presence or absence of metastatic lesions in the parametrial, hypogastric and presacral region than does lymphography.
- 4. An "inlet" view of the pelvis as a routine projection in lymphography is helpful in evaluating subtle changes in the lymph nodes due to metastatic deposits.
- 5. Because of the complementary nature of lymphography, venography and urography, the extent of neoplasm is best evaluated by the 3 procedures combined.
- 6. The detection of metastatic disease in Stages I, II, and III carcinoma of the cervix in 105 operated patients was 80, 90, and 100 per cent, respectively.
- 7. An abnormal venogram, especially with obstruction of the major veins, would seem to indicate a poor prognosis, regardless of the clinical staging of carcinoma of the cervix.

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#### THE VALUE OF THE INLET AND OUTLET VIEWS OF THE PELVIS IN LYMPHOGRAPHY

By K. FRANCIS LEE, M.D.,\* PHILIP J. HODES, M.D.,† and SHU-REN LIN, M.D.‡ PHILADELPHIA, PENNSYLVANIA

IN THE interpretation of lymphograms, difficulty often arises due to superimposition of lymph nodes in the pelvis, especially in the external iliac regions. When the opacified lymph nodes are increased in number and size, their overlapping seriously interferes with detailed analysis of their internal architecture, even in the oblique view.

For better delineation of these pelvic lymph nodes, we have routinely employed inlet (cephalad angled) and outlet (caudad angled) projections of the pelvis in addition to the anteroposterior, lateral and oblique projections for the past several years.1 The value of the angled views will be discussed with illustrative cases.

#### METHOD

I. Inlet or cephalad angled view of the

pelvis. With the patient in the supine position, the x-ray tube is angled 45° towards the head, its central beam being directed to the midsacrum.

2. Outlet or caudad angled view of the pelvis. With the patient in the supine position, the x-ray tube is angled 45° towards the feet, its central beam being directed to the anterior iliac spine.

#### REPORT OF CASES

Case 1. A 40 year old male with a seminoma testis; normal lymphogram.

The inlet view of the pelvis showed excellent separation of the iliac lymph nodes with good delineation of each nodal architecture. The smooth indentation in the superior aspect of one of the external iliac lymph nodes on each side was due to the hilum of the lymph nodes; this should not be mistaken for a metastatic focus (Fig. 1A).

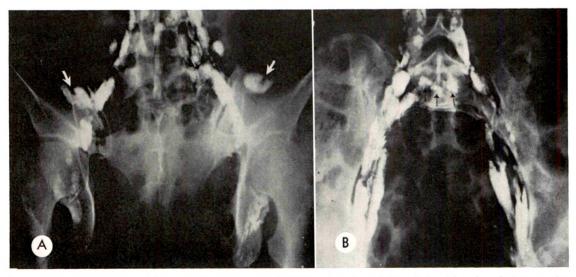


Fig. 1, Case I. Seminoma with normal lymphogram. (A) The inlet view of the pelvis with 45° cephalad angulation of the x-ray tube demonstrates good delineation of the individual lymph nodes without superimposition. The hila of the external iliac lymph nodes are somewhat prominent (arrows); normal variation. (B) The outlet view of the pelvis with 45° caudad angulation of the x-ray tube reveals good delineation of the common iliac lymph nodes, including the lymph nodes of the promontory (arrows).

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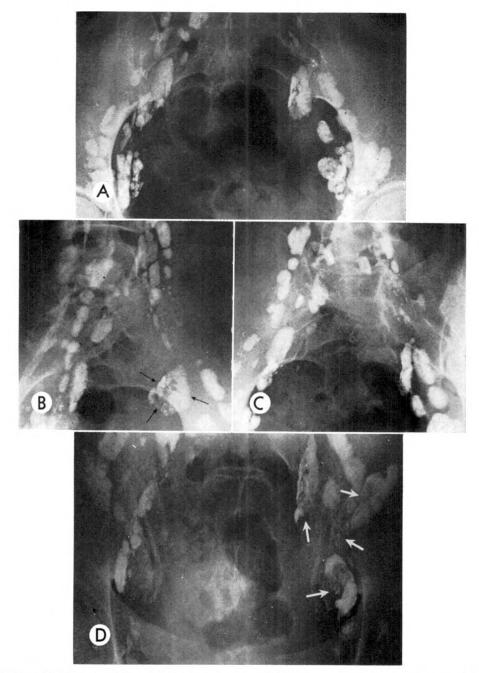


Fig. 2. Case II. Carcinoma of the cervix with metastases. (A) Anteroposterior roentgenogram of the pelvis shows multiple lymph nodes superimposed in the external iliac regions, but no definite abnormality is demonstrated. (B and C) Both oblique views show separation of most of the iliac lymph nodes, but some of the external iliac lymph nodes are still overlapped (arrows). No definite metastases can be diagnosed. (D) The inlet view shows clear-cut delineation of the iliac lymph nodes with multiple irregular filling defects (arrows) on the left side, due to metastases from carcinoma of the uterine cervix.

The outlet view also revealed the 3 chain arrangement of the iliac lymph nodes with good delineation of the common iliac lymph nodes in the axial projection (Fig. 1B).

The patient had an abdominal lymph node dissection following a left orchiectomy. No abnormality was seen in the dissected pelvic or retroperitoneal lymph nodes.

Case II. A 34 year old female with carcinoma of the cervix, Stage I.

Anteroposterior roentgenogram showed superimposition of the several external iliac lymph nodes without definite abnormality (Fig. 2A).

Both oblique views revealed a questionable irregularity in the left external iliac lymph nodes, but no distinct abnormality could be diagnosed. They were initially thought to be due to fatty infiltrations (Fig. 2, B and C).

The inlet view of the pelvis, however, demonstrated unequivocal filling defects involving several iliac lymph nodes on the left side (Fig. 2D).

The diagnosis of metastasis from carcinoma of the cervix was verified at surgery.



Fig. 3. Case III. Carcinoma of the cervix with lymph node metastasis. The inlet view shows a lymph node in the left iliac region with marginal filling defect (black arrows). A smooth defect in the superior aspect of the lymph node (white arrow) represents a hilum of the lymph node (confirmed at surgery). A marginal defect was due to early metastasis.

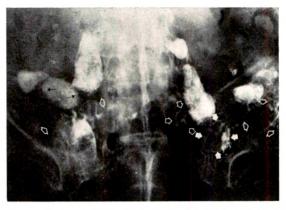


Fig. 4. Case IV. Lymphosarcoma. Multiple enlarged lymph nodes with partial or complete replacement of the parenchyma by lymphomatous growth. Several ring-like shadows are seen in the iliac lymph nodes (white arrows) due to complete neoplastic replacement of the lymph nodes. Multiple enlarged lymph nodes are also noted with a varying degree of neoplastic invasion. The black arrows indicate very early subcapsular involvement of the lymph node.

Case III. A 43 year old female with carcinoma of the cervix, Stage IIA.

The routine lymphograms including the oblique views of the abdomen were thought to be within normal limits.

The inlet view of the pelvis, however, showed irregular marginal filling defects, involving the inferior aspects of one of the external iliac lymph nodes on the left side, due to metastases. This was later proven by surgery. Note a smooth defect in the superior aspect of the same lymph node due to the hilum (Fig. 3).

Case IV. A 63 year old male with lymphosarcoma.

The routine views showed multiple enlarged pelvic lymph nodes with spotted filling defects, but the anatomic details were obscured by superimposition of the lymph nodes.

The inlet view of the pelvis showed multiple white ring-like shadows due to almost complete neoplastic replacement of the lymph nodes with preservation of the subcapsular sinuses, typical of lymphoma. Early lymphomatous change was also noted in the iliac lymph nodes bilaterally (Fig. 4).

Case v. A 23 year old male with Hodgkin's disease.

The inlet view showed multiple defects involving the iliac lymph nodes, suggestive of

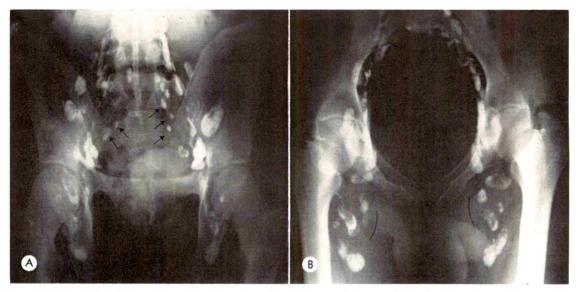


Fig. 5. Case v. Hodgkin's disease. (A) The inlet view shows good demonstration of the external iliac lymph nodes with multiple filling defects. The black arrows indicate the hypogastric lymph nodes. (B) The outlet view shows axial demonstration of the inguinal lymph nodes with central type filling defects; highly suggestive of disseminated lymphoma (curved lines).

early lymphoma. There were several smaller lymph nodes in the medial aspect of the iliac chains, indicating hypogastric lymph nodes (Fig. 5A).

The outlet view demonstrated an excellent delineation of the inguinal lymph nodes with multiple central defects in the axial projection due to lymphomatous involvement (Fig. 5B).

#### DISCUSSION

Gross alteration of the internal structure of the lymph nodes can be readily identified in routine views. In a significant number of the cases, however, superimposition of the lymph nodes in the anteroposterior or even in the oblique views may seriously interfere with proper interpretation of a nodal abnormality. In such instances, the angled views may provide more information. As an added advantage, the angled views provide a 3 dimensional evaluation of the lymph nodes. If the patient is extremely obese, angled views of good quality may not be obtained, and tomography is often necessary.

#### SUMMARY

The advantages of the cephalad and caudad angled views of the pelvis in lymphography are discussed and illus-

trative case reports are presented.

The cephalad or inlet view of the pelvis shows excellent separation of the iliac lymph nodes with good visualization of the nodal outlines in the axial projection. The hila of the iliac lymph nodes can be readily differentiated from pathologic filling defects.

The caudad angled or outlet view of the pelvis provides satisfactory visualization of the inguinal lymph nodes in the axial projection.

The angled views are useful adjunct to the routine views, especially when the lymphographic findings are subtle.

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## PROGNOSIS OF MALIGNANT MELANOMA ACCORDING TO REGIONAL METASTASES\*

By UMBERTO VERONESI, NATALE CASCINELLI and FERDINANDO PREDA

IT IS often difficult to formulate even an orientative prognosis in a case of malignant melanoma because the biologic behavior of this tumor makes the clinical course at times unpredictable. However, some factors, such as the local and regional extent of the disease, the macroscopic and histologic appearance, the site, sex and age can provide good guidance to the prognosis.

The significance of these factors has been studied in a series of 800 cases observed at the National Cancer Institute in Milan, and we have reached the conclusion that: (1) the macroscopic appearance of the primary melanoma, and (2) the condition of the regional lymph nodes are the 2 factors that most directly affect the prognosis; sex, age and site are of marginal importance.

A very simple prognostic guide is careful observation of the primary melanoma. There are good melanomas and bad melanomas.1 The following may be included among the good melanomas: (1) the malignant lentigo, which appears most frequently on the face, is flat, slow growing, and generally remains localized for 10-15 years before spreading; (2) the slow growing contiguous melanoma, generally located on the lower limbs, most often observed in females, which remains localized for a long time before metastasizing to the regional lymph nodes; and (3) the ring melanoma, characterized by very slow growth, which expands eccentrically and simultaneously heals at the center, and rarely metastasizes to the regional lymph nodes.

The main bad melanomas are: (1) the achromic melanoma, marked by a highly malignant clinical course and early lymph node metastases; there are, however, some unpigmented melanomas occurring on the

heel that may have a favorable clinical course and, although they attain considerable size, metastasize late; (2) the ulcerated melanoma, generally of rapid growth; (3) the tumors with satellite nodules; and (4) the very raised tumors, which may occupy a small area of the skin but which tend to metastasize early via the hematogeneous and lymphatic pathways. It should be emphasized, that a very simple but quite useful rule in prognostic evaluation is the fact that the more raised the melanoma the worse the prognosis.

In considering the problem of the extent of the disease, our material was classified according to the TNM system (Table 1).

The prognostic importance of the extent of the primary tumor has been evaluated in

### TABLE I TNM CLASSIFICATION

T—primary tumor

T<sub>0</sub>—no primary tumor present

T<sub>1</sub>—tumor 2 cm. or less in its largest dimension, strictly superficial or exophytic. No satellite nodules

T<sub>2</sub>—tumor more than 2 cm. but not more than 5 cm. in its largest dimension or with minimal infiltration of the dermis, irrespective of size. No satellite nodules

T<sub>3</sub>—tumor more than 5 cm. in its largest dimension or with deep infiltration of the dermis, irrespective of size or with satellite nodules within 5 cm. of the borders of the primary tumor

N—regional lymph nodes

N<sub>0</sub>—no palpable lymph nodes

N<sub>1</sub>—movable homolateral lymph nodes

N<sub>2</sub>—movable contralateral or bilateral lymph nodes

N<sub>3</sub>—fixed lymph nodes

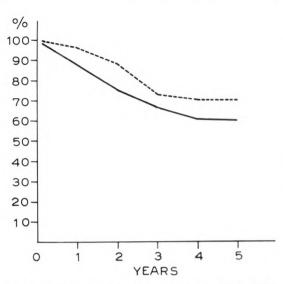
M—distant metastases

M<sub>0</sub>—no evidence of distant metastases

M<sub>1</sub>—distant metastases present, including lymph nodes beyond the region in which the primary tumor is situated, or satellite nodules more than 5 cm. from the border of the primary tumor

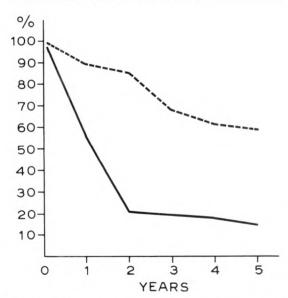
From the National Cancer Institute, Milan, Italy.

<sup>\*</sup> Presented at the Fifty-second Annual Meeting of the American Radium Society, Coronado Island, San Diego, California, March I-5, 1970.



Graph 1. 5-year survival in 91 new cases  $T_1N_0-T_2N_0$  —surgical treatment. ——=  $T_1N_0$ ; ——=  $T_2N_0$ .

a series of 91  $N_0$  new cases. One can see from Graph 1 that the 5-year survival was better in  $T_1$  (less than 2 cm.) than in  $T_2$  (between 2 and 5 cm. in diameter) tumors. However, the key factor in the prognosis of malignant melanoma is the presence of regional lymph node metastases. In the 158  $N_0$  cases treated surgically at our Institute, the 5-year survival was 60 per cent, whereas in the 101 cases with metastases



Graph 2. 5-year survival, 261 cases  $N_0N_1$ —surgical treatment.----=  $N_0$ ; ——=  $N_2$ .



Fig. 1. Metastases of melanoma of the right leg to inguinal and external iliac lymph nodes. This figure shows that the neoplastic tissue is located in the center of the lymph node.

to the regional lymph nodes  $(N_1)$  it was 15 per cent. In the first 2 years the mortality was so high that there seemed to be no difference between the course of the surgically treated cases and the natural course of the untreated melanomas; from the second year on, however, the mortality decreased markedly (Graph 2).

We may say, therefore, that in about 85 per cent of the cases the involvement of the regional lymph nodes was an index of spread of the disease and that metastases beyond the regional lymph nodes, even though not detectable, were already present.

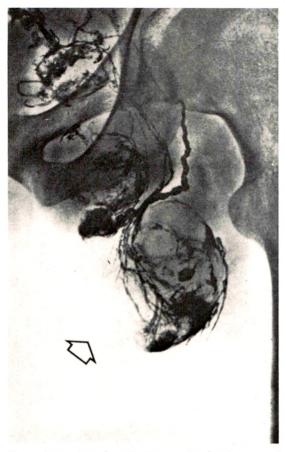
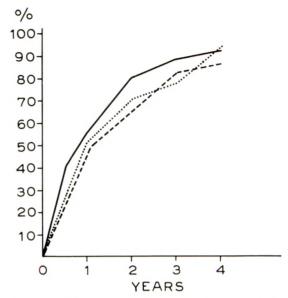


Fig. 2. Large lymph node metastasis of melanoma of the left thigh. The lymph node is almost completely destroyed by neoplastic tissue; however, the marginal sinus is not involved and the contrast material can easily pass through.

Spread of melanoma via the lymph stream in the majority of cases follows anatomic logic. That is to say, it first affects the lymph nodes nearest to the primary tumor and subsequently the more distant ones. But it must be stressed that it is not uncommon to find that a lymph node group has been bypassed, while more distant lymph nodes are affected. In other words, the lymph nodes, which constitute a filter for the spread of tumoral emboli of certain types of carcinoma, such as cutaneous epidermoid carcinoma, are not a good filter for the spread of malignant melanoma.

Moreover, in a study of the lymphatic spread of melanoma by lymphography in a group of 45 cases, we found that invasion of

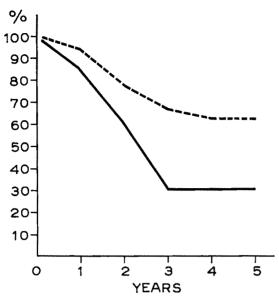


Graph 3. Free interval between treatment of the primary tumor and appearance of regional metastases.----adequate surgery; — = inadequate surgery; ····-=radiotherapy of the primary tumor.

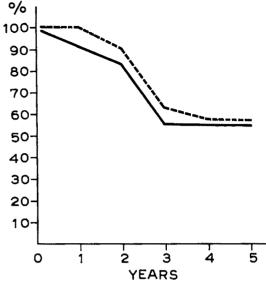
the lymph node by the neoplastic tissue in melanoma does not begin at the marginal sinus as often occurs in epitheliomas, but from the center of the lymph node (Fig. 1; and 2), and therefore even when the lymph node has been replaced by melanoma cells, it is generally compatible with patency of the lymph vessels which are exceptionally obstructed (only 1 of our 45 cases). These findings seem to be in harmony with the histologic investigations, which only exceptionally show extracapsular neoplastic spread, and also with the clinical observation that the lymph node metastases of melanoma remain undetected for a long time.

It is commonly accepted that inadequate surgery of the primary tumor is an adverse factor in prognosis and may produce an explosion of the disease.

Our material has shown that inadequate local treatment has definitely an unfavorable influence as regards local recurrence, but that it does not seem to affect the time of onset of metastases to the regional lymph nodes. The free interval between treatment



Graph 4. 5-year survival, 45 cases N<sub>0</sub> head and neck—surgical treatment. ----= new cases; ——cases previously treated.

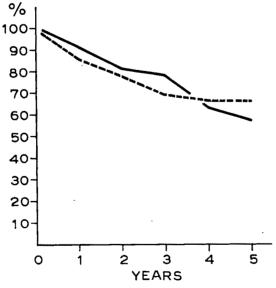


of the primary tumor and the onset of regional lymph node metastases, evaluated in 66 initially  $N_0$  cases that subsequently developed regional metastases, did not seem to be affected by the treatment of the primary tumor (Graph 3).

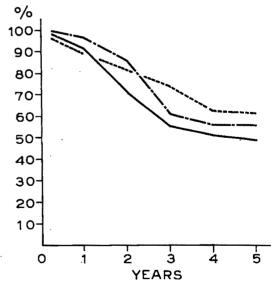
If we consider the survival curves by

site, we can state that inadequate surgice treatment of the primary tumor has an ac verse influence only in melanomas originat ing in the head and neck (Graph 4; 5; and 6)

The site of origin of melanoma seems t be of some importance in the clinical cours of the disease; the data from the literatur



GRAPH 5. 5-year survival, 87 cases N<sub>0</sub> extremities—surgical treatment. ----= new cases;——= cases previously treated.



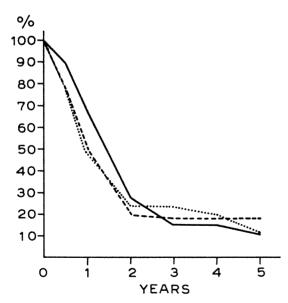
GRAPH 7. 5-year survival, 158 cases No according to site—surgical treatment. ----= extremitie -----= trunk; ----= head and neck.

TABLE II
FREQUENCY OF REGIONAL METASTASES
IN $348 \text{ T}_{1}\text{-T}_{2}$ CASES

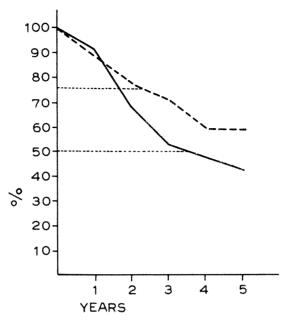
Site	No. of Cases	No. with Regional Metastases	Per Cent	
Head and Neck	89	26	29.2	
Trunk	75	32	42.6	
Extremities	184	62	33.6	
Total	348	120	34.5	

show that melanomas arising on the head and neck have a better prognosis than those arising on the trunk or on the limbs. Our data show that the better over-all prognosis of melanomas originating on the head and neck is related to the fact that they less frequently give rise to regional lymph node metastases (Fig. 2) (Table II). But if we study the 5-year results in the 2 groups, with regional metastases and without regional metastases, we see that the difference disappears (Graph 7; and 8).

As regards long term results according to treatment, the comparison between the

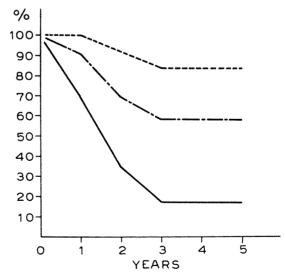


Graph 8. 5-year survival, 101 cases N<sub>1</sub> according to site—surgical treatment. ——= head and neck; ....= trunk; ....= extremities.



Graph 9. Comparison between surgical and radiologic treatment in a series of 200  $N_0$  cases. -----= surgical treatment; ——= radiotherapy.

results of radiotherapy and surgery, in  $N_0$  cases, is in favor of surgery (Graph 9). However, if we consider the results of radiotherapy by site (Graph 10), we can see that for melanomas of the head and neck the results obtained are quite satisfactory.



Graph 10. 5-year survival, 42 cases  $N_0$  according to site—radiotherapy. ----= head and neck; ---= extremities; ----= trunk.

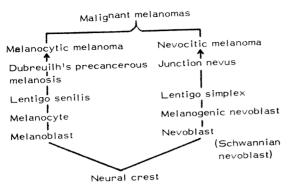
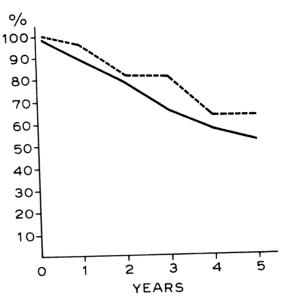


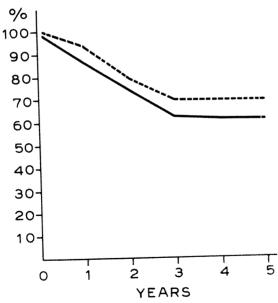
Fig. 3. Two ontogenic pathways leading to the malignant melanomas: malignant melanocytoma and malignant nevocytoma. (Courtesy of Mishima, Cancer, 1967, 20, 632-649.)

This may be due to the fact that the head and neck melanoma often originates from a circumscribed precancerous melanosis. According to Mishima,<sup>2</sup> there are 2 variants of malignant melanoma: the malignant nevocytoma and the malignant melanocytoma; the latter is slower growing, less invasive, is radiosensitive and is frequent in the head and neck. The malignant nevocytoma, on the other hand, originating from

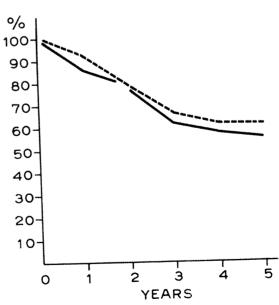


Graph 12. 5-year survival, 63 N<sub>0</sub> cases previously treated—surgical treatment. — = excision only; -----= excision plus prophylactic lymph node dissection.

the melanogenic nevoblast, has the opposite clinical features: is radioresistant and is frequent in the trunk. These 2 types of melanoma are thought to have a different



Graph 11. 5-year survival, 91 N<sub>0</sub> new cases—surgical treatment. — = excision only; ----- excision plus prophylactic lymph node dissection.



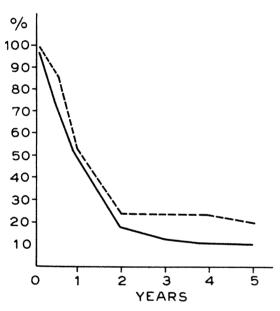
Graph 13. 5-year survival, 158 cases N<sub>0</sub> according to sex—surgical treatment. ----= males; = females.

morphology and ultrastructure. The different DOPA reaction (positive for melanocytoma) differentiates the 2 variants also at biochemical level (Fig. 3). Therefore we concluded that radiotherapy of melanoma may be indicated in the head and neck area where large excisions cannot easily be done, but in the other sites, in our experience, it is not effective.

As regards the dissection of the regional lymph nodes our data cannot give an answer, whether prophylactic or therapeutic dissection is better (Graph 11; and 12).

Concerning sex, our data do not confirm the data from other authors that females have a better prognosis than males (Graph 13; and 14).

As to the choice of the ideal therapy of



Graph 14. 5-year survival, 101 cases N<sub>1</sub> according to sex. ——— = females.

malignant melanoma, there is considerable doubt and the solutions proposed are often contradictory. The extent of surgical removal, the timing of lymph node dissection, the value of preoperative radiotherapy, the indications of perfusion with chemotherapeutic agents and the value of radioactive lymphography are all questions that still

TABLE III

CLINICAL TRIAL OF THE W.H.O. INTERNATIONAL REFERENCE CENTER FOR MALIGNANT MELANOMA

No.	Type	Site and Stage	Begin- ning
ı	Prophylactic versus therapeutic lymph node dissection	Limbs T <sub>1</sub> -T <sub>2</sub> N <sub>0</sub> M <sub>0</sub>	1967
2	Chemotherapy with imidazolcarboxamide	Mı	1968
3	Surgical treatment with or without preoperative irradiation	Trunk T <sub>1</sub> -T <sub>2</sub> N <sub>0</sub>	1970
4	Surgery with or with- out a specific immunization	All sites T <sub>1-3</sub> N <sub>1</sub>	1970
5	Single drug or multiple drug chemotherapy	Mı	1970
6	Surgical treatment with or without regional perfusion	Limbs T <sub>1</sub> -T <sub>2</sub> N <sub>1</sub>	1971

await an answer. The reasons for the uncertainty lie in part in the biologic behavior of these tumors and in part in an incorrect utilization of clinical material.

Melanoblastoma is a rare disease, and the number of observations that can be used for therapeutic trials in any institute is often so small that no objective and final evaluation of the results can be made. Further, the comparison of different series is not satisfactory, partly because the criteria of classification differ widely and partly because the choice of treatment, when it is not preordered, is subject to contingent circumstances that cannot always be identified in a retrospective study. Lastly, not a few difficulties stand in the way of a correct histologic diagnosis, and atypical cases are relatively frequent.

#### CONCLUSION

For these reasons we decided at the Sixth

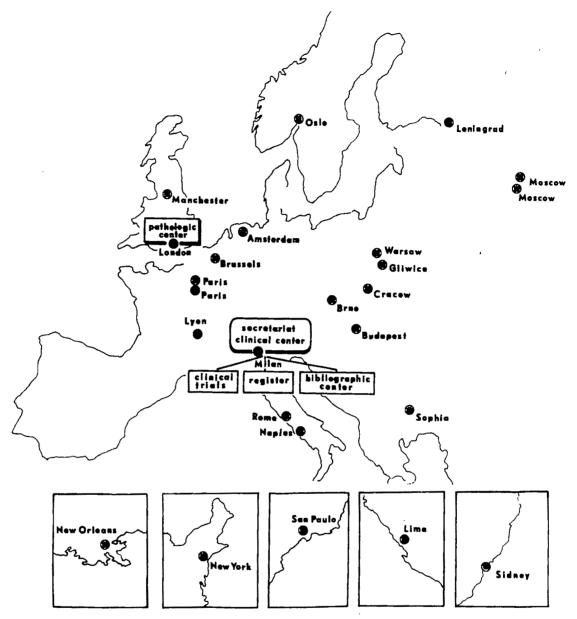


Fig. 4. W.H.O. International Reference Center and Collaborating Centers for the Evaluation of Methods of Diagnosis and Treatment of Malignant Melanoma.

International Conference on Pigmented Cells held in Sofia in 1965 to set up an International Group for the Clinical Study of Melanoma. The Group at present consists of 26 Cancer Institutes in 15 countries; it operates under the control of and is financed by the W.H.O. The Coordinating Center of clinical activity is the National

Cancer Institute in Milan, to which information on all cases of melanoma observed at each Institute is sent. The clinicians rely on the cooperation of a Committee of pathologists, the coordinating center of which is the Royal Marsden Hospital of London. All pathologic material relating to each case is sent there. The final histologic

diagnosis is collective and must be unanimous (Fig. 4).

The objective of the Group is to identify the treatment of choice for melanoma through a series of controlled clinical trials and to study the problem of etiopathogenesis on the basis of all cases of melanoma at any site and stage, which are collectively registered, gathering some 800 cases a year. The controlled therapeutic trials in progress planned for the next few years are summarized in Table III.

This approach to the problem of treating melanoma is, we feel, the most rational and

we are hoping that valuable results will emerge within a few years.

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## MALIGNANT MELANOMA, ITS TREATMENT BY THE ENDOLYMPHATIC ADMINISTRATION OF RADIOACTIVE ISOTOPES\*

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THE proper medica of the nant melanoma has not been devised, THE proper method of treating maligalthough the surgical extirpation of this form of cancer is the best method at present. When a malignant melanoma is located in the region which is in juxtaposition to the primary chain of lymph nodes draining that region, the best method of therapy is to perform a monobloc resection of the primary cancer, the intervening lymphatics, and the lymph nodes to which the melanoma may spread. The great problem arises when a melanoma is located at a great distance from the lymph node basin to which metastases may occur. For example, if a malignant melanoma is located on the foot or lower leg, the problem of how to treat the lymph node bearing area remains problematic. Pack and his associates had advocated that the proper method of adhering to the primary principle of all cancer surgery (i.e., resection of the primary disease, the intervening lymphatic vessels, and the echelon of lymph nodes to which metastases may occur) is to perform a radical amputation18 such as a hip joint disarticulation and radical groin dissection. Such a radical procedure is loathsome both to the patient and the surgeon, and frequently the patient will refuse such a mutilating procedure, even when metastases to the lymph nodes of the groin are clinically evident. The problem becomes more complex when metastases to the lymph node region are not clinically evident. Several courses are available to the physician in such instances. He may either ignore such lymph nodes and adopt a

policy of watchful waiting to see if these lymph nodes become involved by cancer at some later date, or he may elect to perform a discontinuous operation. In the performance of the discontinuous operation, he completely avoids the treatment of metastases which may be present within the lymphatic vessels. Because of this possibility, some surgeons do not perform the lymph node dissection at the same surgical seance with the resection of the primary cancer, but rather wait from 3 weeks to I month in the belief that "in transit" metastases will have traversed the lymphatic vessels in this period, and will have lodged in the lymph nodes. This is strictly hypothetic and one can never be sure regarding the transit time of cancer cells in the lymphatics or whether the lymphatic vessels are clear of these cancer cells. The advent of lymphadenography by Kinmonth and Taylor<sup>15</sup> in 1954 permitted a method of studying the normal dynamics of lymphatic circulation (Fig. 1, A and B). A natural development from diagnostic lymphadenography was the administration of chemotherapeutic agents and/or radioactive isotopes into the lymphatic vessels as a means of delivering a large dose of radiation to the lymph nodes. We were unable to demonstrate any beneficial effects from the endolymphatic administration of cancer chemotherapeutic agents, but the administration of certain radioactive isotopes into lymphatic vessels was shown to result in the delivery of a huge dose of radiation to the lymph nodes with a minimal amount of untoward reactions.

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We have used this procedure for various cancers including lymphomas with encouraging results.

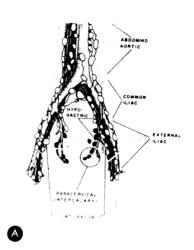
This discussion shall be limited to a progress report regarding our results to date in the over-all treatment of patients bearing malignant melanomas in varying stages of development.

#### TECHNIQUE

The routine technique of Kinmonth and Taylor<sup>15</sup> was utilized, and the isotope used in this investigation was I131 ethiodol—a special preparation of radioactive ethiodol in oil which contains 37 per cent iodine in organic combination with ethyl esters of the fatty acids of poppy seed oil. A certain portion of the stable iodine has been replaced by the I131. This isotope has a maximum beta energy of 0.6 mev. and a maximum penetration in tissue estimated at 2 mm. The major therapeutic effect is from the beta rays with very little, if any, obtained from the gamma rays. The isotope has a half life of 8.5 days which permits protracted irradiation, and the I131 ethiodol has a further advantage of being both diagnostic and therapeutic. Other radioactive nuclides which have been utilized are radioactive gold 198, yttrium 90 microspheres, and chromic phosphates (P32).

This presentation shall be limited to the results obtained with I131 ethiodol. Radioactive chromic phosphates and microspheres (Y90) produced problems of administration, and the radioactive gold was found to be unsuitable because it could not be combined with the ethiodol, and a fair amount of the administered gold was concentrated in the liver. Certain treatment policies evolved as the study progressed, and the results obtained are best described by presenting the data according to the clinical staging of the malignant melanoma. All melanomas were of the invasive type and where a question existed regarding the diagnosis, or if it was simply a so-called "melanoma in situ," such cases were not included in this series.

Stage I are those melanomas where the



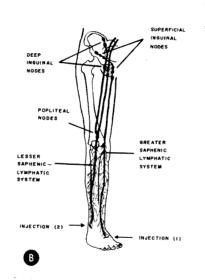


Fig. 1. (A) Anatomy of lower abdominal lymph nodes. (B) Lymphatic vessels of lower extremity. Injection site 1, on dorsum of foot, drains into greater saphenous lymphatic system. Injection site 2, lateral aspect of ankle, drains into lesser saphenous system, into popliteal lymph nodes, and then to inguinal lymph nodes. (By courtesy of Arch. Surg., 1967, 94, 117.)

regional lymph nodes are clinically and roentgenographically negative for evidence of metastases.

Stage II are those melanomas where the regional lymph nodes contain metastases.

Stage III is where there are satellites; *i.e.*, deposits of melanoma throughout the skin of the involved extremity or other evidence of melanoma involving the extremity such as subcutaneous nodules, or deeper nodules.

Stage IV is where there are distant metastases.

#### STAGE I MELANOMAS

The treatment policy for this grade of cancer consists of a wide reaction of the primary melanoma.

Unlike Edwards<sup>9</sup> and his group who do not resect the deep fascia, we firmly believe that the deep fascia should be resected and that the dissection should extend to naked muscle. We cannot accept the claims of Olsen<sup>17</sup> that the resection of the deep fascia has certain disadvantages. It is in this deep fascia that the lymphatics traverse and we routinely remove a much larger

amount of the deep fascia than of the overlying skin. The techniques utilized by our group have been described.<sup>18</sup>

In three weeks to a month after the resection of the primary melanoma, a therapeutic lymphogram is obtained. The reason for the delay is to assure complete healing of the skin graft which is always necessary for melanomas of the extremities, if the excision has been adequate. A theoretic benefit as suggested by Petersen et al.<sup>20</sup> is that the delay will permit time for possible "in transit" metastases to traverse the lymphatic vessels and reach the lymph nodes.

We commence with the injection of the radioactive I<sup>131</sup> ethiodol. I would prefer to start with "cold ethiodol" for diagnostic purpose, but I feel fearful that this may interfere with complete filling of the lymph nodes with the radioactive material. Monitoring is done with a Geiger counter placed

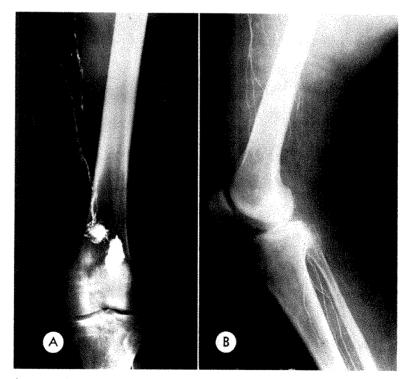


Fig. 2. (A) Lymphogram of normal man demonstrating 2 popliteal lymph nodes. Injection made posterior to internal malleolus. (Courtesy of H. W. Fischer, M.D.) (B) Lymphogram of a patient with melanoma, performed as in A, demonstrating well developed chain of lymphatic vessels coursing popliteal space; no lymph nodes present. Dissection revealed 1 popliteal lymph node completely replaced by fat. (By courtesy of New York State J. Med.)

over the groin or axilla to assure proper flow of the radioactive isotope. Immediately after the completion of the administration of the isotope and 24 hours later diagnostic roentgenograms are taken. Where possible, the lymphatic vessel isolated is one just proximal to the line of resection. In a few instances, we have injected in different areas to assure filling of all lymphatic vessels. The injections in the posterolateral aspects of the foot will permit filling of the popliteal chain of lymph nodes (Fig. 2,  $\mathcal{A}$  and  $\mathcal{B}$ ).

We have previously described the metabolism of the I<sup>131</sup> ethiodol so administered and have shown that the average blood level of I<sup>131</sup> comprises 0.01 per cent of the administered dose per liter and the urine excretes about 1 per cent of the administered dose for 24 hours.<sup>4</sup> These are similar to the results obtained by Edwards.<sup>9</sup>

If the roentgenogram of the lymph nodes is considered negative for evidence of metastases, no further treatments are given, but the patient is followed carefully and repeated roentgenograms of the lymph nodes are taken. If a defect exists within the lymph nodes which might be considered to be a metastasis, the patient is subjected to a dissection of the lymph node bearing area and if metastases are discovered, he is placed in the category of Stage II (Fig. 3).

Dosage and Volume. The dose of  $I^{131}$ ethiodol varies from 40 to 50 mc in 4 ml. for the lower limb and 30 to 40 mc in 2 ml. for the upper limb. Smaller doses are sometimes given if clinically indicated. For example, older patients have an attrition of lymph nodes and there is a freer flow of the isotopes to higher regions in such instances. In patients with pulmonary disease, because of the fact that a certain amount of the isotope reaches the lungs, smaller doses are given as well as smaller volumes. Measurements performed on the lymph nodes regarding the radioactivity have revealed that such dosages will deliver from 50,000 to 100,000 rads  $\beta$  ravs to the lymph nodes (Fig. 4). The technique for obtaining these values has been previously



Fig. 3. Lymphogram of a patient with metastatic melanoma to left inguinal region, taken 5 days after injection of ethiodized oil. Note stagnation of lymphatic vessels and development of collateral circulation where presacral lymph nodes are visualized in midline. Note space-occupying lesions in the inguinal lymph nodes characteristic of metastases. (By courtesy of New York State 7. Med.)

described.4 In those publications we have considered the use of smaller doses of radioactive isotopes, but by gradually increasing the dose, we have found the amounts here described to be adequate and safe. We have observed no complications (to be discussed later), but to avoid the possible spillover of the isotope through the thoracic duct into the lungs, it is essential that the over-all volume given be reduced. In the past, we gave 10 ml. to the lower extremities and 5 to the upper. We have reduced this to a maximum of 4 ml. to the lower extremities and 2 ml. for the upper extremities. With these smaller volumes, approximately 10 per cent of the ad-

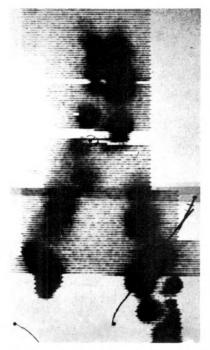


Fig. 4. Scintiscan after the administration of I<sup>131</sup> ethiodol. Note retention of the isotope throughout the pelvic and periaortic lymph nodes.

ministered dose will reach the lungs. Repeated scannings have revealed that the isotope is rapidly eliminated from the lungs. An occasional patient suffers a brief period of slight dyspnea or cough following the treatment, but long-term studies, including pulmonary function tests, have demonstrated to date, no untoward pulmonary reactions. Much longer term follow-ups are, of course, necessary inasmuch as the irradiation to the lungs is a potential hazard of this technique.

#### STAGE II MELANOMAS

In such cases, the primary melanoma is treated the same as for Stage I. Staging is determined either on clinical examination of the patient, or if the lymphogram reveals a space-occupying defect in I of the lymph nodes (Fig. 5). The over-all treatment policy consists of: (I) a wide resection of the primary melanoma, the same as for Stage I; (2) endolymphatic isotope; (3) 2 weeks later a *bloc* dissection of the lymph nodes plus intraarterial administration of

a cancer chemotherapeutic agent (either phenylalanine mustard or actinomycin D). The reason for the delay before performing the surgical resection of the lymph nodes is to permit deterioration of the isotope with its resultant beneficial radiation effect to the tissues and also to reach a safe dose for the operating team. The Atomic Energy Commission recommends a dose of 5 mc to be safe for the operating team, and inasmuch as the biologic half life of I131 ethiodol equals approximately 6 days, a delay from 2 to 3 weeks will permit maximum irradiation to the tissues and the maximum protection to the operating team. The effect of the endolymphatic isotope therapy does not contribute to any increased technical difficulties for the surgeon. The tissue is "sticky" and adheres to itself. This sometimes makes it slightly more difficult to dissect the lymph nodes free from the vessels, but in other instances, it makes it easier to dissect the lymph nodes. We have had no unusual complications resulting from the preoperative internal irradiation. There has been no difference in wound healing from those instances where surgery was performed without the preoperative isotopic administration.



Fig. 5. Lymphogram taken after the administration of I<sup>131</sup> ethiodol. Note defect (arrow) which gave a positive result for involvement of melanoma. At a groin dissection performed after the lymphography there was no evidence of melanoma.

Preoperative external irradiation is often given for varying forms of cancer with reported better results. The same philosophy exists for the external irradiation of cancers of the esophagus, rectum and other internal organs as for the preoperative irradiation delivered by the endolymphatic administration of I131 ethiodol for Stage II melanomas. The irradiation would destroy a large number of the cancer cells and make them less viable in case of spillage. It would irradiate certain deposits of cancer which might be outside the field of surgery and it would irradiate the cancer cells within the lymphatics especially where obstruction has occurred. If any lymph nodes are inadvertently left behind and are not included in the groin or axillary dissection, they would be irradiated (at one time we used chlorophyl I131 ethiodol to visualize better the lymph nodes, but this has been discontinued because of regulations from the Food and Drug Administration). Furthermore, the lymphogram gives diagnostic data regarding the flow within the lymphatics, that is, whether obstruction exists or not, and gives certain data regarding the distribution of the lymph nodes and whether metastases exist within them.

#### STAGE III MELANOMAS

We have treated 5 patients suffering from satellitoses of their extremities, by the endolymphatic administration of radioactive isotopes. Each of these patients had been treated previously by resection of the lymph nodes and the satellitoses developed subsequently. The mechanism for this we believe to be a regurgitation of lymph carrying cancer cells as a result of blockage caused either by tumor or the surgical procedure.1,2 Two of these patients have demonstrated complete disappearance of the satellites and I patient remains clinically free of melanoma 5 years after such treatment. In 2 patients, the nodes involving the inner aspect of the thigh, i.e., the distribution of the lymphatic vessels, disappeared, whereas those involving the lateral aspect of the thigh did not change in appearance. The remaining patient manifested no benefit.

#### STAGE IV MELANOMAS

No beneficial clinical response was observed in our 2 patients treated by I<sup>131</sup> ethiodol delivered via the lymphatics of the feet. Metastases to the lungs, liver or other sites existed and irradiation to the pelvic and periaortic lymph nodes had no demonstrable clinical effect. Both patients died from disseminated melanoma.

#### RESULTS

Table 1 presents our experience with 57 patients suffering from malignant melanoma who were considered candidates for endolymphatic I<sup>131</sup> ethiodol. The data are presented according to the clinical staging of the malignant melanoma. There were 26 patients who were classified as clinical Stage 1, and who remained well and free of evidence of melanoma for the duration of the study. There were 7 who were clinically negative, but who later developed

Table I

EXPERIENCE WITH 57 PATIENTS WITH MALIGNANT MELANOMA WHO WERE CANDIDATES FOR ENDOLYMPHATIC I 131 ETHIODOL THERAPY

Stage	No. of Patients
I. Clinically negative for metastasis to	
lymph nodes and remained well and	
free of metastasis	26
Clinically negative, subsequent de-	
velopment of metastasis	***
Clinically negative, but had a groin	
dissection and the lymph nodes were	
histologically negative	4
Clinically negative, but a false-	
positive lymphogram	2
II. Clinically negative for metastasis,	
lymphogram positive for metastasis	3
Clinically positive and lymphogram	
positive	8
III. Satellitosis and other metastasis to	
involved extremity	5
IV. Distant metastases	2
Total	

TABLE II

MALIGNANT MELANOMA—SURVIVAL RATES OF PATIENTS TREATED WITH ENDOLYMPHATIC I131 ETHIODOL

3-YEAR SURVIVAL RATES Clinical Stages 1 and 11

Clinical Stage	No. of Patients	No. of Deaths	Survival and Free of Disease Over 3 Years (per cent)
1	13	2	85
	6	3	50

metastasis. Four patients were considered clinically negative, but for varying surgical reasons, a lymph node dissection was performed and the lymph nodes were found to be histologically negative for metastases. Two patients were clinically negative, but a false-positive result was obtained on lymphographic studies and they were subjected to a groin dissection.

Of those classified in Stage II, there were 3 patients who were clinically negative for metastases, but whose lymphograms were positive for metastases. Eight patients were clinically positive and the lymphograms were also positive.

There were 5 patients in Stage III and 2 patients with distant metastases.

Table II demonstrates the survival rates of patients treated with endolymphatic I<sup>131</sup> ethiodol over 3 years ago. Those patients who were classified as Stage I and II are presented. Thirteen patients classified as clinical Stage I received this form of

therapy. There were 2 deaths occurring as a result of distant dissemination of the melanoma in this group. The survival rate of those patients who were free of evidence of melanoma for over 3 years is 85 per cent. In clinical Stage 11, there were 6 patients treated. Three developed dissemination of the cancer. The 3 year survival rate in this group is 50 per cent.

Table III presents the over-all results of patients who were treated with I131 ethiodol and later treated by a radical groin dissection. It will be noted that of 4 patients so treated, the lymphogram was interpreted as being positive for evidence of metastasis. but the histology was negative. Only 1 patient developed a recurrence in the region of the groin at the site of the lymph node dissection. The recurrence rate was 25 per cent. No patient in this group developed generalized metastases and none of these patients died as a result of their cancer. In 6 patients whose lymphograms were interpreted as being positive for metastases, which data were confirmed by the histologic examination, none developed local recurrences, but 50 per cent developed generalized evidence of the melanoma and each died from his disease.

It is too early following therapy for the remainder of the patients to make any comments regarding the efficacy of the endolymphatic isotope therapy.

#### DISCUSSION

As a means of determining the reliability of endolymphatic isotope therapy, Ed-

TABLE III patients with malignant melanoma treated by  $I^{131}$  ethiodol and radical groin dissection

	No. of Patients	Recurrence in Lymph Nodes	Recurrence in Lymph Nodes	Metastasis	Per Cent of Patients Who Died
Lymphogram positive- Histology negative Lymphogram positive-	4	Î	25	0	0
Histology positive	6	٥	0	50	50

wards<sup>9</sup> and his co-workers described experimental work performed on VX2 tumor in a host animal—the rabbit. They analyzed their results according to the lymphographic appearance of the lymph nodes, microscopic findings at autopsy, and survival time of the animals.

I. Serial lymphadenographic examination revealed that in the animals in whom the isotope was administered, in a period of 4 weeks after the tumor was implanted, the lymph nodes were heavily infiltrated with cancer. Inasmuch as the maximum range of the  $\beta$  particle of I<sup>131</sup> has a maximum penetration in tissue of 2 mm. with a mean range of 0.3 mm., the expectation of destroying large metastatic deposits is nil. Edwards states, "There was, however, a different pattern of appearance of the two groups with inhibition in growth of the tumor of the treated nodes."9 In the group with the short transplantation-treatment interval the lymphograms revealed a marked shrinkage of the lymph nodes treated with the radioactive isotope and expansion of the lymph nodes in the control group treated with plain lipiodol.

II. Macroscopic and microscopic findings. There was a marked difference in the appearance of the 2 groups in which the treated lymph nodes were markedly smaller than the control group's. They state that the microscopic evaluation of the effects of therapy was difficult in lymph nodes which contained a great deal of tumor; however, in lymph nodes minimally involved, due to a short transplantation-treatment interval the radiation changes of the tumor cells due to I<sup>131</sup> lipiodol could be found even to the complete destruction of the tumor and the lymph nodes.

III. Survival time. There was a marked increase in survival times of the treated animals. Only in the animals with lymph nodes involved with microscopic-sized metastasis was the survival markedly increased, and 25 per cent of these rabbits were cured. Other treated animals eventually died, but far outlived those rabbits who were treated as controls.

We have previously described, on clinical investigation in humans, marked shrinkage of lymph nodes<sup>5</sup> and destruction of malignant melanoma following I<sup>131</sup> ethiodol administration endolymphatically.<sup>4</sup>

In our series of 13 patients in clinical Stage I treated from 3 to 5 years ago, there was a survival rate—free of melanoma—of 85 per cent. This compares with the results obtained from Kinmonth's<sup>15</sup> laboratory as reported by Edwards<sup>9</sup> and his associates. They reported a survival rate of 90.3 per cent for from 2 to 5 years; 89.3 per cent from 3 to 5 years; and an over-all survival rate of 82 per cent from 3 to 5 years. Furthermore, our survival rate of 50 per cent for the 6 patients in clinical Stage II compares with their results of 19 patients in clinical Stage II who manifested a 36.3 per cent survival rate 3 to 5 years. Edwards,9 further evaluated the results from surgery alone at the St. Thomas' Hospital, London, where he performed his investigations, and was able to show that in Stage I cancer, the 3 year survival rate was 59.5 per cent, and in Stage II the survival rate was 12.5 per cent. He further believes that a more relevant comparison of the efficacy of the endolymphatic form of therapy in comparison to surgery alone is the recurrence rate in lymph nodes. In 31 patients, treated by surgery and endolymphatic therapy, 9.7 per cent developed recurrences in the region of the lymph nodes and eventually died. In those treated by surgery alone, of 42 such patients, 15 developed recurrences in the lymph node region and 14 died.

Fully realizing the inadequacy of reporting a very small series of no statistical significance and that a series of 3 year results cannot be compared to a series of 5 year survival rates, Table IV does make such a comparison for an index of clinical accomplishment of endolymphatic isotope therapy. The data for those patients treated by surgery alone were obtained from the files of the Pack Medical Group and represent patients treated by the same technique and for the most part by the

Table IV

COMPARISON OF SURVIVAL RATES OF PATIENTS WITH MALIGNANT MELANOMA TREATED BY SURGERY ALONE OR SURGERY WITH ENDOLYMPHATIC RADIOACTIVE ISOTOPES

Stage	(wide local excision a	ith Surgery Alone nd lymph node dissection)	Treated with Endolymphatic Radioactive Isotopes and Surgery	
	No. of Patients	5 Year Survival Rate	No. of Patients	3 Year Survival Rate
Ι	37	40.5%	13	85%
II	199	14.1%	6	50%

From: Pack, G. T., and Ariel, I. M.: Treatment of malignant melanoma by adequate (radical) surgical resection and radical amputation when indicated. In: Current Surgical Management. J. H. Mulholland, E. M. Ellison and S. R. Friesen, Editors. W. B. Saunders Company, Philadelphia, 1957, pp. 438–446.<sup>19</sup>

same group of surgeons. An index of improvement is noted in those patients who received I<sup>131</sup> ethiodol endolymphatically which appears promising and warrants further clinical trial.

We have observed that approximately 40 per cent of the patients in clinical Stage I will eventually develop metastases to the lymph nodes. We are accordingly convinced that the policy of watchful waiting is not justified.

If the melanoma is in juxtaposition to the lymph node bearing region to which metastases may occur, a dissection of the primary melanoma, the intervening lymphatics and the lymph nodes in continuity is the procedure of choice. If, however, the melanoma is distant from the lymph nodes and an *en bloc* dissection is not technically feasible, a discontinuous operation must be considered; *i.e.*, removal of the primary melanoma, and a groin or axillary dissection. The intervening lymphatics possibly harboring melanoma cells "in transit" or fixed are thus ignored.

We have demonstrated that the discontinuous operation, moreover, is not without hazard.<sup>2</sup> Alterations in lymphatic dynamics occur which favor the "take" or dissemination of the cancer have been observed (Fig. 6; and 7). These consist essentially of a sealing-off of the severed lymphatic vessels which hinders and obstructs lymphatic flow with the development of the following sequence of events:

(1) obstruction of lymphatic channels di-

rects metastases into different channels with their subsequent lodgement in lymph nodes which do not directly drain the primary cancer site; (2) obstruction of lymph

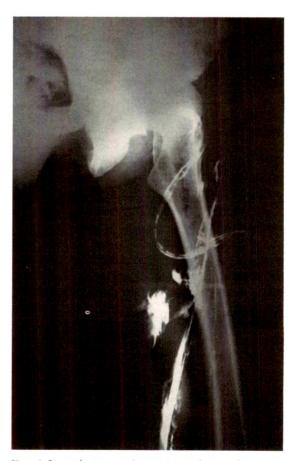


Fig. 6. Lymphogram taken 3 days after performance of radical groin dissection for melanoma. Note injected ethiodized oil removed by means of a hemovac within wound site. Note lymphocele. (By courtesy of New York State J. Med.)

nodes by metastases causes the formation of collateral lymphatic channels, presenting unusual locations for the lodgement of metastases; (3) the collateral lymphatic network may be so extensive, including the perivascular lymphatics of Wallace, as to offer a means of conveyance for cancer cells freely to almost any part of the body; (4) lymphatic obstruction produces lymphatic hypertension; lymphatic stagnation favors the "take" of "in transit" metastases; (5) lymphatic regurgitation within the dermal network is a mechanism, whereby cancer

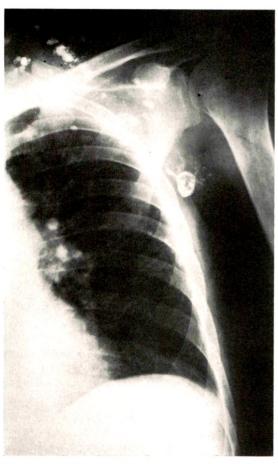


Fig. 7. Lymphogram demonstrating reconstituted lymphatic circulation. Regenerated lymphatic vessels communicate freely with supraclavicular lymph nodes; new collateral circulation developed with internal mammary chain of lymph nodes. Note residual lymph nodes in axilla harboring metastatic melanoma. Left radical axillary dissection for melanoma performed 2 years previously elsewhere. (By courtesy of New York State J. Med.)

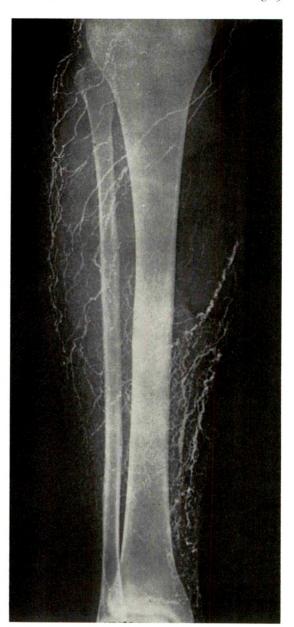


Fig. 8. Marked lymphedema following radical groin dissection for melanoma with development of extensive network of lymphatic vessels.

cells, especially melanoma, are transmitted to the tiny superficial lymphatics to lodge and grow, producing satellitoses (Fig. 8); and (6) lymphatic obstruction encourages the function of lymphaticovascular communications; this may be one method whereby melanoma cells gain entrance into the vascular circulation.

Metastases in the lymphatic vessels and lymph nodes may produce a majority of the foregoing alterations, which are markedly aggravated by the discontinuous performance of either a groin or axillary lymph node dissection.

# COMPARISON OF COMPLICATIONS FROM A LYMPH NODE RESECTION WITH THOSE RESULTING FROM ENDOLYMPHATIC ISOTOPE INJECTION

Fortner, Booher and Pack<sup>11</sup> described their complications following groin dissections for melanoma. Three patients had serious complications (1 cardiac arrest with death, 1 patient had a severed ureter and bladder and 1 had a tear in a major vein). Local complications consisted of necrosis of skin flaps (64.5 per cent) necessitating skin grafts (23 per cent). Moreover, a significant number of patients had swelling of the affected limb which at times can be severe. The incidence of satellitoses (skin metastases) varied from 9 to 25 per cent.

The complications following isotope therapy have been minimal. Slight transitory edema and pyrexia for 1 to 2 days have been observed in one-third of our patients. We have a 10 per cent failure rate to administer a proper therapeutic dose due to technical problems. At first, we had difficulty with the healing of the incision, but pouring a liter of saline solution over the wound after the removal of the catheter and before the wound is suture closed has completely prevented this complication. One patient developed a transient rash possibly due to sensitivity to iodine. Five per cent of the patients had a mild cough for a period of 1 to 3 days. No pulmonary complications have been observed and patients have been followed for up to 3 years with repeated pulmonary function tests.

It is thus demonstrable that the surgical extirpation of lymph nodes is not without hazard, particularly when the operation is done in a discontinuous manner and pro-

duces certain local complications. Internal irradiation, apparently when given in the dose range described herein, exerts no demonstrable effect upon lymphatic dynamics.<sup>5</sup> It does not cause blockage of lymphatic flow, nor does it result in the formation of collateral lymphatic channels for unpredictable dissemination of cancer cells throughout the body. Even after the administration of therapeutic doses of irradiation, the filtration stability of the residual lymph nodes seems to be intact.

The continued application of these clinical investigations, adhering to the principles of therapy above described, are warranted.

#### SUMMARY AND CONCLUSIONS

The treatment of malignant melanoma by a combination of surgery and endolymphatic isotopic therapy is based on experimental evidence that the dose of irradiation delivered by this route will destroy microscopic-sized deposits of cancer.4 In lymph nodes bearing cancer, there is marked destruction of melanoma in the lymph nodes after the endolymphatic administration of 40 mc of I131 ethiodol. This has been accomplished with no demonstrable interference to lymph flow due to marked differences in sensitivity to irradiation of the lymph nodes and the lymphatic vessels. The lymph nodes are radiosensitive, and the lymphatic vessels are radioresistant.

Endolymphatically administered I<sup>131</sup> ethiodol delivers a sufficient irradiation (50,000 to 100,000 rads β) to the lymph nodes in humans to destroy microscopic-sized deposits of melanoma cells lodged within the lymph nodes. The primary melanoma is treated by orthodox surgical techniques. Patients classified as clinical Stage I receive no additional surgery, but receive I<sup>131</sup> endolymphatically, and are thus spared the trauma of a radical axillary or groin dissection and their ensuing complications. A 3 year survival rate in a small group of patients with clinical Stage I of 85 per cent is encouraging.

Patients with Stage II melanoma are

treated by a combination of endolymphatic isotopes and surgical removal of the primary melanoma and the lymph nodes. The penetration of the irradiation from the administered isotope is not sufficient to depend upon such irradiation to destroy the cancer. In such instances, irradiation of lymph nodes outside the field of surgery, irradiation of any lymph nodes inadvertently left behind and irradiation to cancer cells within the lymphatics offer an additional dimension in the treatment of these patients. A 3 year survival rate of 50 per cent in a small group of patients so treated seems promising.

Several patients with satellitoses have markedly benefited from endolymphatic isotope therapy.

Two patients with distant metastases so treated have shown no improvement and endolymphatic isotopes are not indicated for such patients.

Only by continued clinical trial, preferably on a randomized basis, can the exact role of the endolymphatic administration of radioisotopes be obtained. In England, the Medical Research Council is sponsoring such a study. At the Hunterian Lecture delivered at the Royal College of Surgeons in London, Edwards spoke about the accomplishments of endolymphatic isotopes for malignant melanoma and concluded his lecture with the following note: "There is no reason why this illness cannot be fully documented in each case arising in Great Britain and the details analysed by experts in this field. It would surely be an advance in the concept of treating malignant disease and something of which Hunter would have approved."9

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# SURVIVAL AFTER SURGICAL EXCISION OF SINGLE METASTATIC BRAIN TUMORS\*

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N SOME radiotherapy centers, the appearance of central nervous system signs in a patient with a histologically verified malignant neoplasm outside the central nervous system, present or past, is assumed to indicate the development of metastatic brain disease. Such a patient may be given radiotherapy, with or without roentgenographic demonstration of an intracranial mass, and without benefit of surgical decompression and tissue diagnosis. In view of the experience documented in this report, it is our policy to make a thorough search for a surgically treatable lesion in every patient suspected of metastatic brain tumor. The investigation usually includes routine skull, chest, and skeletal survey roentgenograms, bone marrow study, echoencephalography, electroencephalography, and scintiphotographic brain imaging using technetium 99m. If this search reveals no evidence of widespread disease or severe disability, appropriate cerebral angiography is then performed.

In 51 such patients seen within the past 10 years, the single metastatic lesion was excised surgically. During 1969, we reported on 41 of these patients, 39 of whom were treated by surgical excision without radiation therapy, and compared our experience with the previously published experience of others. Within the 20 months between closure of that series and the end of 1969, 10 additional patients with single metastatic lesions in the brain were treated surgically. The cumulative data are shown below, in the same format as before for comparison. Two of the patients in our

original series had received radiation therapy to the brain. We stated then that we were considering further use of this modality for certain patients; 8 of the 10 additional patients have been so treated. The combined experience tends, in our view, to corroborate the belief expressed in our former report, that unwarranted pessimism has obscured evaluation of the results of surgical treatment of the single metastatic brain lesion.

In addition, we call attention here to an exceptional group of 12 patients in whom the circumstances and clinical appearance strongly suggested metastatic brain disease, but who were found at craniotomy to have unrelated lesions, a number of them benign and operable. Eight such patients had been noted during the previous 10 years;<sup>2</sup> 4 additional cases (half again as many) were found, perhaps as a result of sharpened awareness, during the ensuing year and a half.

Where the outcome of surgical treatment of single brain metastases had encouraged us, the discovery of this high percentage of nonmetastatic lesions warned us to pursue the differential clinical diagnosis, surgical exploration, and tissue diagnosis of every patient with cancer who is suspected of having a metastatic lesion of the brain.

#### PRESENT SERIES

Fifty-one patients with a single metastatic brain lesion were treated by craniotomy at Kaiser Foundation Hospital, Oakland, between October 1959 and December 31, 1969. As shown in Table 1, only 4 were

<sup>\*</sup> Presented at the Fifty-second Annual Meeting of the American Radium Society, Coronado Island, San Diego, California, March 1-5, 1970.

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Table I  $\begin{tabular}{ll} \textbf{AGE AT ONSET OF SYMPTOMS FROM SINGLE BRAIN } \\ \textbf{METASTASIS AND SEX DISTRIBUTION} \\ \textbf{OF 5I PATIENTS} \end{tabular}$ 

Age (yr.)	Male	Female
10–19		I
20-29		I
30-39	1	I
40-49	7	4
50-59	8	10
60-69	12	4
70-79	2	
Total	30	21

younger than 40, and 2 were older than 70 years.

In evaluating the results of craniotomy, the site and type of the primary tumor were taken into account (Table II). Bronchogenic carcinoma, one of the most rapidly lethal of all neoplasms, was the primary tumor in more than half (26) of the cases; breast carcinoma was the primary lesion in the next largest number (9 cases). A neoplasm that is held by many observers to carry a better prognosis (renal carcinoma) was the primary lesion in only 2 of our series.

As seen in Table III, the majority (27) of the lesions were in the distribution of the middle cerebral artery: parietal, frontoparietal, or temporoparietal lobe.

Each patient was studied by one or more of the following: electroencephalography, echoencephalography, or scintiphotography

TABLE II
PRIMARY TUMOR: TYPE AND SITE

Carcinoma		4I
Lung	26	
Breast	9	
Kidney	2	
Corpus uteri	I	
Colon	3	
Lymphoma		2
Mediastinal	I	
Retroperitoneal	I	
Melanoma		3
Axilla	I	
Adrenal	I	
Subungual (toe)	I	
Unknown		5

TABLE III
SITE OF BRAIN METASTASIS

Parietal	16
Frontal	10
Frontoparietal	7
Cerebellar	6
Temporoparietal	4
Temporal	à
Frontotemporal	2
Skull, dura, sinus	1
Parasellar	1

with Tc<sup>99m</sup>. In 50 patients, one or more types of contrast study was performed (Table IV). In 30 cases angiography alone, and in 4 cases pneumography alone sufficed; in 16 cases multiple lesions could not be ruled out until both studies were used.

The interval between onset of symptoms from the primary lesion, and of those from the brain metastasis, is related to the type and site of the primary tumor in Table v. Only the symptoms of lung and breast carcinoma preceded those of the brain metastasis by an appreciable interval. Indeed, the clinical disturbance that initiated investigation for tumor was due to the metastatic brain lesion in 60 per cent of the cases (Table vi).

Neoplastic tissue was removed at craniotomy from 49 patients. In each of these, an effort was made to excise the entire metastatic lesion, and to provide decompression by removing the adjacent lobe. Excision of the metastasis and primary lesion was achieved in only 4 of the patients with bronchogenic carcinoma.

The sites of postoperative radiation therapy are shown in Table vII.

SURVIVAL SPAN

Our operative mortality rate (defined as

TABLE IV
DIAGNOSTIC CONTRAST STUDIES

Angiography	30
Pneumography	
(pneumoencephalography,	
ventriculography)	4
Angiography and pneumography	16

	Table $V$	
INTERVAL FROM CLINICAL	EVIDENCE OF PRIMARY TUMOR	TO SIGNS OF BRAIN METASTASIS

Origin of Tumor	None	o−6 Mo.	6–12 Mo.	ı Yr.	1-2 Yr.	2-3 Yr.	3-8 Yr
Carcinoma				**************************************		***************************************	
Lung (26)	15	3	3	2	2		r
Breast (9)	ĺ	2	1	2	<del></del>	ī	2
Kidney (2)	2			_		•	_
Corpus uteri (1)	ı						
Colon (3)	1				2		
Lymphoma					~		
Mediastinal (1)	ı						
Retroperitoneal (1)	ı						
Melanoma							
Axilla (1)		1					
Adrenal (1)	1						
Subungual (toe) (1)							T
Unknown (5)	5						

death within 2 weeks after craniotomy) was 12 per cent (6 patients).

Among 15 individuals who lived longer than 1 year after craniotomy (Table VIII), 1 has survived the operation 9 years. The primary lesion was in the lung in 8 of these 15 long term survivors—nearly one-third of the total group with bronchogenic carcinoma; it was in the breast in 5, or half of those with mammary carcinoma (Table IX).

Of 11 patients still living at the time of report, 4 have survived craniotomy longer than 1 year (Table x). The postcraniotomy

TABLE VI
FIRST TUMOR IDENTIFIED: PRIMARY OR METASTATIC

	Primary (No.)	Metastatio (No.)
Carcinoma (41)		
Lung (26)	g	17
Breast (9)	7	2
Kidney (2)	,	2
Corpus uteri (1)	0	1
Colon (3)	2	1
Lymphoma (2)		-
Mediastinal (1)		1
Retroperitoneal (1)		ī
Melanoma (3)		•
Axilla (1)	1	
Adrenal (1)	•	ŗ
Subungual (toe) (1)	ĭ	•
Unknown (5)	•	5

TABLE VII

NUMBER OF PATIENTS RECEIVING
POSTCRANIOTOMY RADIOTHERAPY

	Lung	Brain	Lung and Brain
Before October 1959 October 1959 to	2	I	I
December 31, 1969		5	3

survival spans of the 4 current survivors who had lung cancer range from 11 months to 4 years. The 2 survivors who had breast cancer have lived 9 months and 3 years respectively since brain lesion excision.

# SURVIVAL QUALITY

Fourty-four patients left the hospital alive. Of these, 40 had good to excellent sensorimotor function, mental and intellectual integrity. Complications in the 4 patients were partial aphasia and hemiparesis (2 patients), mild hemiparesis (1 patient), and homonymous hemianopsia (1 patient).

#### NONMETASTATIC LESIONS

In addition to providing a satisfactory means of palliation in many patients with devastating illness, our investigations have directed attention to the occasional impor-

Table VIII
LENGTH OF SURVIVAL AFTER CRANIOTOMY

		2 Wk. 6 Mo.				4 <sup>-5</sup> Yr.	6–7 Yr.	7-8 Yr.	9-10 Yr.
Carcinoma					 		 		 
Lung (26)	4	12	2	6		I			1
Breast (9)	ï	2	1	3	2				
Kidney (2)		I	1	Ť					
Corpus uteri (1)			1						
Colon (3)		3							
Lymphoma		•							
Mediastinal (1)		1							
Retroperitoneal (1)				1					
Melanoma									
Axilla (1)			1						
Adrenal (1)	1								
Subungual (toe) (1)				1					
Unknown (5)		1	4						

tant exception to the general rule that, if symptoms referable to the brain arise in a patient known to have malignant neoplasia, an intracranial metastasis has developed. We reported<sup>2</sup> 8, and are here reporting 4 additional cases of nonmetastatic brain disease in such patients (Table x1). The brain lesions actually found in these 12 cases are related to the type and site of the

TABLE IX

SITE OF PRIMARY NEOPLASM IN PATIENTS
SURVIVING CRANIOTOMY LONGER THAN I YEAR

Carcinoma	
Lung	8
Breast	5
Lymphoma	_
Retroperitoneal	1
Melanoma	
Subungual (toe)	I
Total	15

TABLE X

PRIMARY SITE IN PATIENTS ALIVE
AT TIME OF STUDY

Lung	4 (11 mo., 15 mo., 17 mo., 4 yr.)
Breast	2 ( 9 mo., 3 yr.)
Colon	2 ( I mo., 3 mo.)
Unknown	3 ( 9 mo., 9 mo., 11 mo.)
Total	11 alive

former neoplasms, and to the duration of symptoms from the intracranial lesions, in Table XII. The outcome in each patient is indicated in Table XIII.

#### CONCLUSIONS

The evidence from these 51 cases of single metastatic brain tumor and 12 cases of suspected but not actual metastasis leads us to suggest 5 points:

1. When one is confronted with clinical

Table XI

INTERVAL FROM TREATMENT FOR NEOPLASM TO ONSET OF SYMPTOMS FROM UNRELATED BRAIN LESION

Case No.	Age (yr.)	Sex	Former Neoplasm Site	Inter- val (yr.)
I	57	F	Carcinoma, breast	7
2	49	$\mathbf{F}$	Carcinoma, breast	2
3	63	$\mathbf{F}$	Carcinoma, breast	8
4	62	$\mathbf{F}$	Carcinoma, breast	6
5 6	37	$\mathbf{F}$	Melanoma, leg	2
6	73	M	Melanoma, back	4
7	48	$\mathbf{F}$	Carcinoma, vocal cord	6
8	38	$\mathbf{F}$	Carcinoma, thyroid	9
9	76	$\mathbf{F}$	Carcinoma, colon	3
IO	42	M	Fibrosarcoma, sacrum	3 8
II	72	$\mathbf{F}$	Carcinoma, breast	12
12	66	$\mathbf{F}$	Carcinoma, breast	8

manifestations suggesting intracranial metastatic neoplasia, one should defer therapeutic decision until adequate information is in hand. Blanket recommendation to allow the disease to take its course on the assumption that any action is useless, surgical treatment on clinical grounds alone, "blind" administration of irradiation or chemotherapy is not warranted.

2. Adequate investigation includes all or several of the following: skull, chest, and skeletal roentgenographic survey, bone marrow study, echoencephalography, electroencephalography, and radioisotope brain

Table XII

DURATION OF CENTRAL NERVOUS SYSTEM SYMPTOMS AND BRAIN LESION FOUND IN 12 PATIENTS
WITH UNRELATED NEOPLASTIC PRIMARY DISEASE

Case No.	Former Lesion	Duration of Brain Lesion Symptoms (mo.)	Brain Lesion
I	Carcinoma, breast	3	Meningioma, sphenoid ridge
2	Carcinoma, breast	3	Chronic subdural hematoma
3	Carcinoma, breast	8	Chronic subdural hematoma
4	Carcinoma, breast	3	Enchondroma, middle cranial fossa
5	Melanoma, leg	6	Protoplasmic astrocytoma, tem-
6	Melanoma, back	I	Subcortical hematoma
7	Carcinoma, vocal cord	2	Glioblastoma, parietal lobe
8	Carcinoma, thyroid	3	Meningioma, sphenoid ridge
9	Carcinoma, colon	2	Meningioma
IO	Fibrosarcoma, sacrum	ı yr.	Meningioma
11	Carcinoma, breast	4 da.	Aneurysm with clot
12	Carcinoma, breast	Ï	Astrocytoma

Table XIII

SURVIVAL AND NEUROLOGIC STATUS OF 12 PATIENTS WITH BRAIN LESION UNRELATED

TO PREVIOUS NEOPLASM

Case No.	Lesion	Sur	iniotomy vival Months	or	Neurologic Status
1	Meningioma, sphenoid ridge	8	7*	L	Moderate left hyper-reflexia
2	Chronic subdural hematoma	0	6	L	Intact
3	Chronic subdural hematoma	8	4	L	Intact
4	Enchondroma	6	3	L	Intact; suggested recurrence
5	Protoplasmic astrocytoma	I	2	D	,
6	Subcortical hematomat	0	0	D	
7	Glioblastoma	0	8	D	
8	Meningioma, sphenoid ridge	0	3	L	Intact
9	Meningioma	1	3 6	L	Intact; recurrence 1969; meningeal sarcoma irradiated
10	Meningioma	6	0	L	Intact
II	Aneurysm with clot	6	0	L	Intact
12	Astrocytoma	6	0	D	(No autopsy)

<sup>\*</sup> Lost to follow-up.

<sup>†</sup> Refused craniotomy.

imaging. If these indicate that surgical treatment may prove worthwhile, angiography, pneumography, or both should be performed to delineate the lesion.

- 3. In many patients, total surgical excision of the tumor with internal decompression can prolong life for significant periods. The neurologic quality of survival has been good to excellent in the great majority of the survivors in our series.
- 4. Although only 10 of our 51 patients received postoperative irradiation to the head, and 8 of these 10 were treated within the last year and a half so that firm conclusions cannot be drawn, the inference is that survival may be further prolonged and improved by the judicious use of this modality.
- 5. A number of factors, including emphatically the discovery of benign or other fully operable brain lesions at craniotomy, warn that "blind" radiation therapy or chemotherapy without prior tissue confirmation and surgical decompression may be detrimental.

#### SUMMARY

In 51 patients, single metastatic brain lesions were excised. Only 10 (8 of these within the last 1½ years) received postoperative radiation therapy to the brain. More than half of the 51 patients had carcinoma of the lung, the primary neoplasm

conceded by many observers to have the worst prognosis; yet 15 survived craniotomy longer than 1 year and 11 were alive at time of review. In addition, 12 other patients with histologically confirmed primary carcinoma, suspected of having intracranial metastatic disease, proved to have nonmetastatic lesions at the time of craniotomy, 9 of which were completely benign. There is thus substantial reason for considering the surgical removal of single metastatic brain tumors, or of lesions suspected to be in this category.

It is suggested that the patient with known primary malignant neoplasm, in whom symptoms of central or cerebellar dysfunction arise, be fully investigated for an operable lesion. At least a tissue diagnosis should be made, and preferably surgical excision of the brain lesion should be attempted, before institution of radiotherapy.

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# A REVIEW OF EXPERIENCE WITH IRRADIATION OF BRAIN METASTASIS\*

By LOURDES Z. NISCE, M.D., BASIL S. HILARIS, M.D., and FLORENCE C. H. CHU, M.D. NEW YORK, NEW YORK

IN 1954, Chao and associates¹ first published the results of irradiation of brain metastasis in 38 patients who were treated in the Department of Radiation Therapy at Memorial Hospital, New York City, from 1949 through 1953. Of these, 24, or 64 per cent showed worthwhile palliation. In a subsequent report in 1961, Chu and Hilaris,² based on the analysis of 218 patients treated between the years 1954 and 1958, re-emphasized the value of irradiation in the management of patients with intracranial metastases.

The purpose of this study is: (1) to compare the results of brain irradiation of a more recent series of patients with previous experiences; (2) to determine the effect of higher dose levels and better radiation qualities on the response rate and duration of remission; and (3) to evaluate the influence of adjuvant corticosteroids.

# MATERIAL

From February 1961 to January 1968, 560 patients with brain metastases from various primary lesions were accepted for whole brain irradiation. The types of primary tumors are presented in Table 1.

TABLE I
PRIMARY LESION SITES

	No. of Patients	Per Cent
Breast	222	39
Lung	141	25
Melanoma	45	8
Others	152	28
		and the state of t
Total	560	100

The largest group of 220 patients (39 per cent) had carcinoma of the breast. The second largest group, 141 patients (25 per cent) had bronchogenic carcinoma. Patients with melanomas comprised 8 per cent. Other primary lesions (28 per cent) included lymphomas (reticulum cell sarcoma and lymphosarcoma), genitourinary and gynecologic cancers, bone and soft tissue sarcomas, gastrointestinal cancers, head and neck cancers, and 8 unknown primary lesions. The youngest patient was I year old and the oldest was 82 years old. The largest number of patients ranged from 50 to 60 years of age. With mammary carcinoma contributing the bulk of cases, the sex ratio was 3 females: 2 males.

The symptoms and signs are presented in Table II. Most patients had multiple neurologic deficits. The predominant findings were motor deficits, disorientation, sensory deficits and aphasia. Frequently,

TABLE II
SIGNS AND SYMPTOMS

	No. Per	Cent
	,	
Motor deficit	417	75
Disorientation, lethargy, coma	208	41
Headaches	168	33
Sensory deficits	159	28
Slurred speech, aphasia	120	21
Nystagmus	106	19
Seizures	101	18
Nausea and vomiting	99	17
Visual field involvement	84	15
Diplopia	81	14
Blurred disks	78	14
Papilledema	74	13
Dizziness	43	8

<sup>\*</sup> Presented in part at the Fifty-second Annual Meeting of the American Radium Society, Coronado Island, San Diego, California, March 1-5, 1970.

From the Department of Radiation Therapy, Memorial Hospital for Cancer and Allied Diseases, New York, New York.

TABLE III
DIAGNOSTIC WORK-UP

	No. of Patients	Per Cent
Neurologic examination	541	96
Lumbar puncture	519	92
Electroencephalography	445	79
Arteriography	249	44
Isotope scanning	173	31
Pneumoencephalography	<u>58</u>	10
Echoencephalography	29	5

patients were comatose at the time irradiation was started. There were 47 patients, or 8 per cent, who presented with symptoms and signs of brain metastasis before the primary tumor was diagnosed. Of these, 60 per cent were subsequently found to have bronchogenic carcinoma.

Practically all patients had a neurologic examination performed by the staff of the Neurology Service. Various diagnostic procedures were employed (Table III). With a few exceptions, lumbar puncture was routinely done. The majority of patients also had electroencephalography. More recently, neurologic work-up also includes other procedures such as arteriography, pneumoencephalography, isotope scanning, and echography.

# RADIATION THERAPY

All patients received total brain irradiation utilizing parallel opposed lateral fields averaging 14×20 cm. in size. About one-half of the patients received orthovoltage irradiation. The other half were treated with I mev., 2 mev., 6 mev. roentgen ray or telecobalt irradiation. After July 1966, only telecobalt therapy and 6 mev. linear accelerator therapy were utilized. When 250 kvp. roentgen rays were used, bolus bags were packed around the head to improve the dose distribution. Figure 1 shows the isodose distribution of a 250 kvp. roentgen ray treatment. The dose to the brain varied from 100 per cent to 130 per cent, which was not very homogeneous, but was considered fairly satisfac-

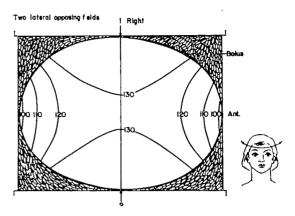


Fig. 1. Isodose distribution of 250 kvp. total brain irradiation. Two lateral opposing fields with bolus; 70 cm. target skin distance.

tory. With megavoltage roentgen ray or telecobalt irradiation, no bolus was used. Figure 2 demonstrates the isodose distribution of a 2 mev. roentgen ray irradiation of the head through 2 lateral opposing fields. The dose ranges were from 134 per cent to 140 per cent. Originally, low initial doses of 75 to 100 rads were given, but with the general use of corticosteroids since 1962, the initial doses ranged from 200 to 250 rads. The majority of patients received 1,000 rads per week, to a total dose of 3,000 to 4,000 rads. The steroid used was usually prednisone, 60 mg. daily for the first 5 days, 40 mg. daily for a few additional days, and then a maintenance daily

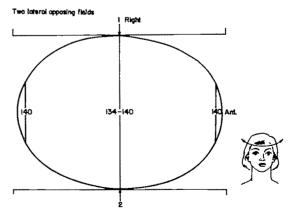


Fig. 2. Isodose distribution of 2 mev. roentgen ray total brain irradiation. Two lateral opposing fields with no bolus; 71.5 cm. target skin distance.

dose of 20 mg. throughout the remaining course of irradiation.

#### RESULTS

Of the 560 patients accepted for treatment, 45 were lost to follow-up, and 139 died of various causes before completion of the prescribed course (Table IV). The causes of death, aside from brain metastasis, included hepatic failure, pancytopenia, bacteremia, septicemia, hemorrhage, intestinal obstruction, cardiac arrest, electrolytes imbalance, and pulmonary embolism. The remaining 376 patients were available for evaluation. The results were analyzed according to the response rate, duration of remission, and length of survival. In addition, the influence of corticosteroids, radiation quality, tumor dose, and the type of primary tumor were also considered.

Of the 376 patients evaluated, 302, or 80 per cent, improved after a course of irradiation; the mean duration of remission was 5 months and the median duration, 3 months (Table v). Almost one-half of these patients showed major improvement in their status, so that those with severe incapacitation improved at least to the point where they were able to care for themselves. Those with lesser involvement recovered completely, so that they were able to lead a normal or near normal life. The average duration of remission was 6 months in patients with breast carcinoma, 5 months in patients with bronchogenic carcinoma, and 3 months in patients with malignant melanoma. The longest remission was 5 years. If the patients who failed to complete treatment, and who were lost to

Table IV

OVER-ALL EXPERIENCE
(1961-1968)

	No. of Patients
Total number accepted	560
Incomplete treatment	139
Lost to follow-up	45
Available for evaluation	376

TABLE V
RESULTS OF IRRADIATION

Primary Site	No. of Pa- tients Evalu- ated	No. of Patients Improved	Mean Dura- tion (mo.)	Median Dura- tion (mo.)
Breast	165	132(80%)	6	3
Lung	93	77(83%)	5	3
Melanoma	27	22(81%)	3	2
Others	91	71(78%)	5	3
Total	376	302(80%)	5	3

follow-up were also considered as failures, the over-all response rate of the entire group of 560 patients was 54 per cent.

There were 47 patients who required a second course of total brain irradiation because of recurrence of symptoms. Twentyone, or 45 per cent improved. The mean duration of improvement was 4 months. Only 3 patients received a third course of total brain irradiation.

An attempt was made to compare the results of treatment with orthovoltage irradiation and supervoltage irradiation. Except for less scalp reaction with supervoltage irradiation, no statistical difference in the response rate or duration of response was discernible. An attempt was also made to correlate the results with different dose levels. Since the majority of patients in this series received either 3,000 rads in 3 to 4 weeks or 3,500 to 4,000 rads in 3 to 4 weeks, comparison was made between these 2 groups. There was no appreciable difference. The use of adjuvant corticosteroids produced immediate symptomatic improvement in the vast majority of patients and facilitated the administration of irradiation. Corticosteroids, however, did not influence the over-all results of irradiation.

The survival data were analyzed. None of the patients who failed to complete the prescribed course of treatment lived beyond 3 months. In those patients who completed the course of irradiation, but failed to respond, 96 per cent died within 9 months

of irradiation. In contrast, in those patients who showed favorable response to irradiation, 20 per cent lived 1 year and 10 per cent lived 2 years. When the survival results were analyzed according to the types of primary tumors, 25 per cent of patients with breast carcinoma survived 1 year, as compared to 15 per cent in patients with bronchogenic carcinoma, and 10 per cent in patients with malignant melanomas (Fig. 3).

Sixty per cent of 91 patients who came to autopsy had multiple metastatic foci in the brain. All 12 patients with malignant melanoma showed multiple lesions scattered throughout the brain (Table vI).

### DISCUSSION

In our previous series<sup>2</sup> of 218 patients treated for intracranial metastases in the 1950s, 35 did not complete the prescribed treatment, 12 completed the prescribed course of treatment, but were lost to follow-up, and 158 patients were available for evaluation. Of the latter group, 123, or 78 per cent, showed improvement for a mean duration of 5 months (Table vII). In this series of 560 patients treated in the 1960s, 139 did not complete the prescribed course of irradiation, 45 were lost to follow-up and 376 patients were available for evaluation. Again, in those patients who received a full course of therapy, a response rate of approximately 80 per

TABLE VI
POSTMORTEM BRAIN FINDINGS

Primary Lesion	of	Per Cent of Multiple Metastases
Breast	26	65
Lung	23	43
Melanoma	12	100
Bone and soft tissue	9	56
Genitourinary-gynecologic	7	71
Rectal	7	29
Lymphoma	7	43
Total	91	60

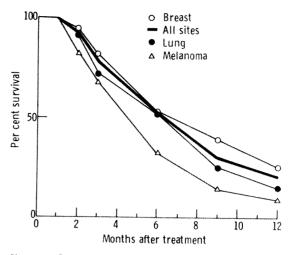


Fig. 3. One year survival of 302 patients with brain metastases who responded to irradiation.

cent was obtained, and the mean duration of remission was 5 months. The addition of corticosteroids, the change over from orthovoltage irradiation to megavoltage irradiation, and the increase of the total tumor dose from 3,000 rads in 3 to 4 weeks to 3,500 to 4,000 rads in 3 to 4 weeks did not materially change the over-all results.

From the over-all experience, analyzing the results of irradiation of 816 patients from our 3 series, plus a similar series of 108 patients reported by Order et al., a pattern appears to have emerged. Approximately one-fifth of the patients with brain metastasis will not be able to complete the prescribed course of irradiation because their general status deteriorates rapidly. Most of these patients die of their disease within a short period of time. Approximately one-half of all patients, and three-fourths of

TABLE VII

COMPARISON OF RESULTS

Years	No. of Pa- tients Ac- cepted	No. of Pa- tients Evalu- ated	No. of Patients Improved	Mean Dura- tion (mo.)
1954-1958	218	158	123(78%)	5
1961-1968	560	376	302(80%)	5

those who received a full course of irradiation will be benefited.

The use of corticosteroids prior to irradiation almost invariably produces immediate and sometimes dramatic improvements of neurologic symptoms. These improvements, however, are short-lived and it is necessary to institute irradiation to control the intracranial tumors. The mechanism of action of corticosteroids in relieving brain symptoms is not yet clear, but probably related to its anti-inflammatory and anti-edema properties. In recent years corticosteroids have been used routinely at Memorial Hospital before and during irradiation in the management of patients with intracranial metastases.

Since most patients who had autopsy showed multiple lesions in the brain, our policy has been to irradiate the whole head when intracranial metastasis was diagnosed. From our previous experience doses below 2,750 rads in 3 weeks usually resulted in poor response. In this study a dose in the order of 3,500 rads, delivered in 3 to 4 weeks appeared to produce satisfactory results and, therefore, we continue to recommend this dose for the management of patients with intracranial metastases.

## CONCLUSIONS AND SUMMARY

A new series of 560 patients with intracranial metastases, treated by irradiation, has been reviewed and the results are reported.

In this series worthwhile palliation was obtained in 54 per cent of the total number of patients, and 80 per cent of the 376 patients who completed the planned course of irradiation, and were available for evaluation. The mean duration of re-

mission was 5 months and the median duration 3 months.

The use of supervoltage irradiation and adjuvant corticosteroids reduced radiation reactions and permitted easier administration of irradiation, but there was no influence on the over-all response rate or duration of response when compared to 250 kvp. irradiation without adjuvant corticosteroids. The results were comparable with those reported previously.

Since most patients have multiple metastatic foci in brain, we continue to advocate total brain irradiation to a dose of 3,500 rads in 3 to 4 weeks.

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The authors are grateful to Dr. Giulio D'Angio, Chairman of the Department of Radiation Therapy, for his advice in the preparation of this paper. We are also indebted to our colleagues in Neurology, Surgery, Medicine and Radiation Therapy for their cooperation and assistance in the management of the patients included in this study.

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# THE MANAGEMENT OF METASTASES TO THE BRABY IRRADIATION AND CORTICOSTEROIDS\*

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METASTASIS to the brain is a disabling, common, and usually fatal complication of many types of cancer. Most measures previously tried for palliation have produced only temporary benefit. Corticosteroids and irradiation have been used alone and in combination with some success.<sup>2</sup>

This study was designed to try to answer two questions: (1) Can as much palliation be offered by corticosteroids alone as with corticosteroids and irradiation? (2) If a remission is obtained with the combination, do corticosteroids need to be continued to prolong remission?

### PATIENT SELECTION

Patients were accepted for study who had histologically proven cancer and evidence of parenchymal metastasis to the cerebrum and/or cerebellum. Such evidence included clinical symptoms and signs together with abnormalities of such investigations as radioisotope brain scans, electroencephalograms, echo encephalograms, angiograms and spinal fluid chemistry and cytology. Care was taken to exclude patients with focal signs due to metabolic encephalopathy. Histologic proof of brain metastasis was not required; patients thought to have had all gross tumor surgically excised were not eligible. The extent

of tumor in the rest of the body was considered for the purposes of the proto

#### STUDY DESIGN

Patients eligible for study were assig by closed envelope technique to I c treatments.

- (A) Prednisone 40 mg. daily in dividoses by mouth for 4 weeks. Following the dose was reduced to 30 mg. daily continued indefinitely until there evidence of progression. The patient then removed from study.
- (B) Prednisone 40 mg. daily in divi doses for 4 weeks. External Co60 t therapy with a source skin distance of cm. using opposing lateral fields design to include the entire brain was started a the patient had received prednisone for to 72 hours. Daily mid-plane increme of 2,000 r, to a total tissue dose of  $4,\infty$ in the elapsed time of 22-29 days, w given. At the end of irradiation, patie who entered remission were rando assigned in a double blind fashion to ceive either prednisone 30 mg. daily or identical placebo. The initial random tion sequence was designed to ensure t twice as many patients received the co bination of corticosteroids and irradian as received prednisone alone.

Before and frequently during treatme

Bruce I. Shnider, M.D., Chairman.

Other members who entered patients into this study were: Bruce I. Shnider, M.D., Georgetown University Medical Division, General Hospital, Department of Medicine, Georgetown University School of Medicine, Washington, D.C.; Albert Schilling, Poston University Medical Center, University Hospital, Boston, Massachusetts; Melvin J. Krant, M.D., Medical Service, Le Shattuck Hospital, Department of Medicine, Tufts Medical School, Boston, Massachusetts; and Pierre Band, M.D., Department Medicine, University of Alberta, Edmonton, Alberta, Canada.

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We wish to thank Dr. Samuel S. Stubbs of the Upjohn Company, Kalamazoo, Michigan for generous supplies of Prednison Placebo.

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notation was made of performance status using an arbitrary scale of from 0, normal performance, to 4, completely bedridden. The degree of any neurologic deficit due to metastasis was recorded on a scale using 0, no deficit, to 4, a complete deficit. The observers did not know the identity of the pills that patients in the second part of the study were taking.

#### RESULTS

Forty-eight patients were studied. Primary sites of tumor were: lung 30, breast 7, melanoma 4, kidney 3 and miscellaneous 4.

#### TOXICITY

The treatments were well tolerated. Side effects of corticosteroids were noted, but in only 2 patients did their severity necessitate stopping treatment. The irradiation produced virtually complete alopecia starting at about 3 weeks, but all patients had been forewarned of this.

# ANTITUMOR RESULTS

Patients were classified as having a remission on the purely clinical grounds of an improvement in their "performance status" of at least 2 points coupled with a similar degree of improvement in any of their neurologic deficits. The incidence of remissions induced by each treatment is shown in Table 1. The duration of remissions is shown in Table 11.

Seventeen patients who had a remission from the combination treatment were

TABLE I
INCIDENCE OF REMISSIONS

D. C.	Treatment		
Primary Site	P.+Irradiation	P. Alone	
Lung Breast	14/19	7/11 5/5	
Other Sites	3/8	9/3 0/3	
	18/28 (61%)	12/19 (63%)	

P. = Prednisone.

Table II

MEDIAN DURATION OF REMISSIONS IN WEEKS

	Treatment		
Primary Site	P.+Irradia- tion	P. Alone	
Lung	13	5	
Breast	15*	8	
Other sites	8	0	

P. = Prednisone.

entered into the second part of the study. Seven received placebo and 10 received prednisone. The median duration of remission for the prednisone group was 5 weeks and for the placebo group 11 weeks. The range was very wide and the variability of response precludes judgement that this difference was not due to chance. Two patients who relapsed while taking placebo improved again when prednisone was reinstituted.

The duration of survival measured from time of onset of treatment for the intracerebral metastasis is shown in Table III. The actual times varied from 3 days to 53 weeks. No relationship was evident between the duration of known previous disease and subsequent survival.

TABLE III

MEDIAN SURVIVAL FROM START OF

TREATMENT IN WEEKS

	Treatment		
Primary Site	P.+Irra- diation	P. Alone	
Lung	20	8*	
Breast	10	20*	
Other sites	14	2	
A 11	appeared to the second of the	********	
All	14	10	
Over-all Survival	13		
Survival of Responders	15		

P - Pradnisona

<sup>\*</sup>Only 1 patient was represented in this group.

<sup>\* 2</sup> patients with carcinoma of the lung and 3 with carcinoma o, the breast in the group indicated under prednisone alone had subsequently received irradiation.

#### DISCUSSION

Accurate evaluation of response of brain tumors by our present laboratory techniques is unreliable. We therefore used only clinical criteria. These were purposely made strict so that only patients who had unequivocal benefit would be included as responders. Better and more objective methods of evaluation are sorely needed.

The onset of remission was usually noted within 48 hours. The incidence of remissions was similar in both groups of patients. There was a suggestion that the remissions induced by the combination treatment were longer than those from prednisone alone (Table II). This effect was probably due to the irradiation since the continuation of prednisone in patients classified as responders who had received the combination did not prolong the remission. In addition, the duration of survival, although short, was somewhat longer in those patients who received the combination.

There was only minimal apparent prolongation of survival of the patients classified as responders when compared to that of the entire group. The smallness of this difference may be due to the fact that many of the patients classified as nonresponders did actually derive clinical benefit which was not sufficient for them to be classified as responders, but was sufficient to prolong their survival. This point might have been answered by including a third group, no treatment, into the initial randomization. It is likely that such a group would have a significantly shorter survival than either of the two studied groups.<sup>1</sup>

The results indicate that a combination of irradiation and prednisone offers only a slight advantage over prednisone alone. This hardly justifies the expense, work and inconvenience to the patient and his family of a 4 week course of irradiation taking up about a third of his final days. We plan further studies designed to test the efficacy of much shorter courses of irradiation.

#### SUMMARY

- 1. The combination of irradiation of the brain and oral prednisone offers only slightly better results in terms of duration of remission and survival than oral prednisone alone in the management of metastatic cancer of the brain.
- 2. In patients treated with the combination who enter remission, there is probably no advantage to continuing prednisone prophylactically.
- 3. On subsequent relapse, re-use of prednisone can sometimes be effective.

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# GLIOBLASTOMA MULTIFORME

# AN ANALYSIS OF THE RESULTS OF POSTOPERATIVE RADIO-THERAPY ALONE *VERSUS* RADIOTHERAPY AND CONCOMITANT 5-FLUOROURACIL\*

(A Prospective Randomized Study of 32 Cases)

By ROBERT W. EDLAND, M.D.,† MANUCHER JAVID, M.D.,‡ and FRED J. ANSFIELD, M.D.§

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VER the past decade several clinical and basic research articles have appeared in the literature concerning the possible additive or potentiating effects of 5fluorouracil (5-FU) on radiation therapy of certain neoplasms, although most of the studies are not prospectively randomized and there is little conclusive evidence concerning the ultimate effects on survival. 1,2,4,8,9,14,22 In addition, while there have been numerous articles concerning the effects of combined therapy of head and neck, lung and bladder neoplasms, 6,11,12,18 there is little information concerning the effects of combined chemotherapy and radiotherapy upon primary malignant brain tumors. In an attempt to evaluate these parameters, especially with reference to intracranial neoplasms, a prospectively randomized study of the effects of 5-FU and concomitant radiotherapy on the postoperative survival of patients with documented glioblastoma multiforme was undertaken at the University of Wisconsin Medical Center during the period January 1962 through December 1966. This was a cooperative study among the Divisions of Neurological Surgery, Radiotherapy and Clinical Oncology.

#### MATERIAL AND TREATMENT POLICIES

During the indicated period 32 patients were prospectively randomized and entered into this series. Seventeen patients received radical supervoltage radiotherapy and 15 were treated with radical supervoltage

radiotherapy and concomitant 5-FU therapy. This study was not specifically designed to prospectively attempt to evaluate the merits of routine postoperative radiotherapy so that a surgery only group was not added to the randomization. No patients were admitted to this study who were 77 years of age or older or gave a prior documented history of a malignant neoplasm, other than skin cancer.

The tumor grades, classified by our Department of Surgical Pathology according to Kernohan into astrocytoma Grade 3 and Grade 4 (glioblastoma multiforme), were fairly comparable in both groups (Table 1), although the over-all incidence of Grade 3 tumors is higher than reported in most series.<sup>20</sup> The tumor location was supratentorial in all cases in this series as one might expect (Table II). All cases were surgically verified, and an attempt at gross complete removal was made in all but 2 patients in the radiotherapy group and 3 patients in the combined therapy group. These 5 patients, however, were biopsied. All patients originally entered into this randomized study have been included for analysis and no patient has been lost to detailed followup evaluation. Seven females were treated by radiotherapy alone and 4 female patients received combined 5-FU and radiation therapy. The 2:1 incidence of males to females conforms to the usual sex distribution reported in most series. The average patient age in the radiotherapy only group was 49 years (30-63), and 50

<sup>\*</sup> Presented at the Seventieth Annual Meeting of the American Roentgen Ray Society, Washington, D.C., September 30-October 3, 1969.

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Table I

DISTRIBUTION OF PATIENTS BY TUMOR GRADE
IN BOTH TREATMENT GROUPS

Treatment Group	Gra		
Treatment Group	3	4	
Radiotherapy Combined Therapy	6 8	11 7	
Total	14	18	

years (19-66) in the group receiving combined therapy.

### RADIOTHERAPY TECHNIQUE

The vast majority of patients were treated on our cobalt 60 teletherapy unit, half value layer (HVL) 12 mm. Pb at a source skin distance (SSD) of 95 cm. Three patients in each treatment group were treated on our 1 mev. resonance transformer unit, HVL 3.4 mm. Pb, at target skin distance of 70 cm. In order to vary as few parameters as possible, the radiotherapy techniques were kept relatively simple and uniform. Parallel opposing coplanar portals usually measuring 12×18 cm. were employed to bring the total supratentorial brain dose to a minimum of 5,000 rads in most cases, over 6 to 7 weeks.

Sixteen patients in the irradiation only group completed the full course of radiotherapy. Except for I patient who developed a severe wound infection after receiving a tumor dose of only 1,700 rads, the remaining patients received an average tumor dose of 4,940 rads minimum (4,000-5,170) over an average of 42 days (34-58). Fourteen patients receiving radiotherapy and 5-FU completed the full course of combined therapy. One patient in this group died of postresectional complications after a tumor dose of only 460 rads had been delivered. The remaining combined therapy patients received an average tumor dose of 4,930 rads minimum (4,340-5,090) over an average of 45 days (34-52). It is interesting to note that the concomitant administration

Table II LOCATION OF TUMOR (PRIMARY)

Site	Radio- therapy	Combine Therapy
Frontal	2	4
Frontotemporal	1	ī
Frontoparietal	4	2
Parietal	2	0
Temporoparietal	2	1
Parietooccipital	I	1
Temporal	3	6
Occipital	2	

of 5-FU did not result in a requirement increased radiotherapy protraction or significant reduction in total dosage.

# CHEMOTHERAPY TECHNIQUE

The 5-fluorouracil (5-FU) was admir tered intravenously by the rapid "pu injection technique" to the 15 patie randomized to receive the drug. A sir "course" was given, the initial "full do of 10 mg./kg. being injected on the f day of radiotherapy and for 2 subsequ days with a "half dose" of 5 mg./kg. the fourth day to provide a full "load dose." The 5-FU in concentrated for (50 mg./cc.) was always injected before radiotherapeutic treatment (usually 30 minutes prior to exposure) in order to st dardize the technique and eliminate : possible variance due to timing of admitration of the drug and the exposure ionizing radiation, although there is as no direct evidence to indicate that thi necessary for this agent since it does appear to be a true "radiosensitizer." that time it was our feeling that the flu inated pyrimidines had to be given to point of toxicity in order to be clinically fective. Also there is considerable clin and basic evidence that there is more c radation of 5-FU when given as a con uous slow drip than as a single dose. 16,17

Subsequently, subject to manifestati of toxicity such as oral mucosal ulcerati diarrhea, and leukopenia below 3,0 "half-doses" (5 mg./kg.) were administered 3 times weekly as tolerated during the course of concomitant supervoltage radiotherapy. The range of doses tolerated, considering 2 "half-doses" as I "full dose," ranged between 4 and 15 "full doses" (average 9 doses) before significant toxicity supervened. No prolonged complications outside the field of irradiation or apparently directly related acute deaths were encountered with this chemotherapeutic technique.

Acute toxicity from the combined therapy program as employed in our series was not overly severe, but was encountered to a degree in all but 4 patients, since the administration of 5-FU in general was pushed to toxicity. Leukopenia (less than 3,000) was noted in only I case. Due to the radiotherapy, significant alopecia, of course, was noted to a degree in all cases completing therapy, confined to the treatment portals. Eight patients developed diarrhea, varying in severity from mild symptoms in the majority to a moderately severe diarrhea in 2 cases. This was the most common clinical factor resulting in temporary or permanent cessation of 5-FU therapy, although it was usually responsive to symptomatic measures. Significant persistent stomatitis was the cause for discontinuing chemotherapy in I case.

#### RESULTS

Since the evaluation of quality of postoperative radiotherapy effects is quite subjective, the results of this investigation have been gauged primarily on survival. The duration of symptoms before craniotomy was relatively short in both treatment groups varying from 1-8 months (average 3.0) in the radiotherapy only group to 1-6 months (average 2.6) in the group receiving combined therapy. This is consistent with most series presented in the literature. Frankel and German<sup>10</sup> report an average duration of symptoms of <6 months in 70 per cent of their patients with glioblastoma multiforme. The interval from surgery to institution of radiotherapy,

although relatively short in the majority of cases (1-2 weeks), varied somewhat throughout the study, so that survival time has been measured from the day of surgical exploration (diagnosis). Initially the survival figures appear somewhat more impressive in the radiotherapy only group, with a crossover noted in the absolute cumulative survivals at 12 months (Fig. 1). There is a relative survival plateau for the patients receiving combined therapy through 21 months and then both survival curves are maintained by our 2 living patients at 27 (combined therapy) and 37 (radiation only) months post surgery. The average survival for the entire group was 11.6 months and no statistically significant difference in survival can be detected for the 2 postoperative therapy regimens under investigation. The initial apparent more rapid demise of patients completing a course of combined 5-FU and radiotherapy has been noted in results obtained from combined therapy in other sites, but, other than increased over-all toxicity, no specific factor or factors responsible for this phenomenon have been elicited.

Despite its grossly subjective nature, an evaluation of caliber of survival or "useful life" was attempted (Table III). A post therapy course classified as "excellent" or "good" was noted in 18 patients. Significant improvement was noted in 13 patients classified as showing "good" results, and 5 patients returned to gainful employment or normal former occupations for periods varying from 4 to 35 months and were classified as achieving an "excellent" result. Minimal improvement classified as a "fair" result was noted in 7 patients, and 7 patients who exhibited no improvement clinically or symptomatically were classified as "poor" results. Seventeen patients manifested evidence of neurologic defects following surgery, and 10 patients still exhibited paresis or paralysis after radiotherapy (Table IV). Postirradiation convulsions were noted in 2 patients who received combined therapy, and 4 patients demonstrated persistent visual defects following therapy.

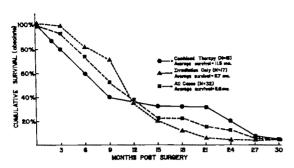


Fig. 1. Composite survival curves for both treatment groups comprising this study.

The caliber of survival and incidence of post therapy residuals were not significantly different in the 2 post surgical treatment groups under evaluation. Autopsies were obtained in 6 cases (3 in each treatment group) and all revealed residual tumor. No evidence of spread outside the central nervous system was encountered in any of our patients.

# DISCUSSION

The use of chemotherapeutic agents in the treatment of malignant neoplasms of the central nervous system has been evaluated by several workers. Davis and Shumway employed Thio-TEPA for metastatic brain tumors with only fair palliation. Llewellyn and Creech<sup>15</sup> have studied the effects of perfusion of glioblastoma multiforme with various agents (TEM, Thio-TEPA, vinleukoblastin) in 24 patients. It was their opinion that tumors are not eradicated by perfusion with the chemotherapeutic agents presently available and that life was not prolonged. Woodhall et al. 21 stated that perfusion of a glioblastoma multiforme by nitrogen mustard in a dose

TABLE III
EVALUATION OF CALIBER OF SURVIVAL

Treatment Group	Excel- lent*	Good	Fair	Poor†
Radiotherapy Only Combined Therapy	3 2	7 6	4 3	3 4
Total	5	13	7	7

<sup>\*</sup> Returned to normal occupation.

of 1.5 mg./kg. probably would ablate the tumor, but would also destroy the hemisphere and ultimately cause the death of the patient. Most chemotherapeutic approaches to the treatment of primary or secondary brain tumors have been via direct infusion or perfusion routes. 19 While Brennan and Vaitkevicius<sup>8</sup> reported no improvement in 2 patients with glioblastoma multiforme treated with systemic 5-FU (15 mg./kg.) alone, it was our plan to randomly and prospectively evaluate the effect of concomitant systemic chemotherapy upon the postoperative radiotherapeutic management of patients with glioblastoma multiforme.

During the period that this clinical study was in progress, Mukherjee et al. 16,17 reported basic work on the metabolism and distribution of 5-FU-2C<sub>14</sub> within the central nervous system. This information was based upon in vivo human studies which included biopsy as well as postmortem specimens. The slow appearance and gradual increase of radioactivity in the cerebral spinal fluid (CSF) of these human patients indicates that either the drug or its meta-

TABLE IV
POST THERAPY RESIDUAL

Treatment Group	Postsurgical Neurologic Defects	Postirradiation Paralysis or Paresis	Postirradiation Convulsions	Persistent Visual Defect
Radiation Only	9	6	0	2
Combined Therapy	8	4	2	2
Total	17	10	2	4

<sup>†</sup> Little or no response.

bolic products are entering the CSF. The levels, however, in the plasma were maintained at a much higher level than in the CSF and it appears that there is no free diffusion of the drug across the blood-brain barrier after intravenous administration. In that study, although the specific activity in some astrocytomas was high, the ability of this type of tumor to convert the drug into "active" or "lethal" nucleotides was poor and the conversion was not greater in central nervous system tumors than in the normal surrounding tissues. Increasing specific activity did, however, appear to be related to the cellularity and anaplasticity of the tumor. Our present randomized clinical series supports the isotopically labeled studies in that 5-FU is ineffective either alone or in conjunction with ionizing radiation in the management of highly malignant astrocytomas.

Despite the lack of improvement in longevity or caliber of survival in patients with proven glioblastoma multiforme who received 5-FU and postoperative radiotherapy over postoperative radiotherapy alone, there is an apparent improvement in longevity for the entire group of patients reported in the literature. Taveras et al.20 report a survival of 7-14 months from first symptom to death in patients receiving no definitive treatment. Elvidge, Penfield and Cone<sup>7</sup> report an average survival of 8.5 months with surgery alone and our over-all average survival was 11.6 months. The total cumulative survival from diagnosis for all patients in this randomized series is indicated in Table v. It must be pointed out, however, that this is a selected series in which only I patient entered died during the early phase of postsurgical radiotherapy. Also since surgery alone was not entered into the randomization, any addition of postsurgical radiotherapy to prolongation of life cannot be verified from this series. While we would agree with Taveras et al.20 that at the present time probably nothing better than surgery and irradiation can be offered as specific therapy, a study involving the prospective

TABLE V

COMPOSITE SURVIVAL STATISTICS\*

Interval (mo.)	Surviving Fraction	Percentage
6	24/32	75
12	12/32	37.5
18	7/32	22
24†	4/32	12.5

\* Surgical diagnosis to death.

randomization of patients with proven glioblastoma multiforme into groups receiving only incomplete but as extensive removal as feasible, and those receiving incomplete resection and high dose supervoltage radiotherapy has been undertaken in an attempt to further answer this question.

#### SUMMARY AND CONCLUSIONS

Between January 1962 and December 1966, 32 patients with a histologically confirmed diagnosis of astrocytoma Grade 3 or 4 (glioblastoma multiforme) were entered into a cooperative, prospectively randomized study to compare the effects of postoperative, high dose, supervoltage radiotherapy alone (17 cases) versus a similar course of postoperative radiotherapy and concomitant systemic 5-fluorouracil chemotherapy (15 cases).

The average survival from diagnosis (incomplete removal) was 11.7 months in the radiotherapy only group and 11.5 months in the combined therapy group.

Two patients are still alive, I at 37 months treated by irradiation alone and I at 26 months who received combined therapy.

We conclude that combined therapy with 5-fluorouracil offers no advantage, from the standpoint of duration or caliber of survival, over high dose postoperative radiotherapy alone in the management of patients with glioblastoma multiforme.

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<sup>† 2</sup> patients alive > 2 years (26 mo., 37 mo.).

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# RADIOTHERAPY OF PRIMARY LYMPHOMA OF THE ORBIT\*

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THERE are few recent reports<sup>1,9,10,12</sup> in the literature concerning the treatment, course, and prognosis of primary lymphoma of the orbit. Although different aspects of the disease are emphasized in these reports, no one study offers details of treatment and analysis of results in a series of reasonable size.

## MATERIAL

The records of 33 patients with primary lymphoma of the orbit treated from 1938-1968 at this institution were reviewed. Both private and clinic patients were included. Excluded from this retrospective study were patients who had leukemia or generalized lymphoma at the time of orbital involvement. In cases where the hospital records were incomplete, an attempt was made to contact the referring physician and the patient to determine the patient's present status. This resulted in follow-up information within the last year of the study on 27 of 33 patients. Results were evaluated from the date of initiation of therapy to the last examination of, or communication with the patient. Cases in which this interval was less than I year were excluded from this study.

The patients' ages at the time of diagnosis ranged from 19 to 77 years with a mean age of 55 years. There were 20 females and 13 males.

All patients had a surgical biopsy. The predominant pathologic diagnosis was lymphosarcoma, lymphocytic cell type, with lymphosarcoma, reticulum cell type being considerably less common (Table 1).

Several patients had more than one site involved and 7 patients had bilateral lesions. Eighteen lesions involved the lids, 12 the conjunctiva and 24 the intraorbital region. Of the latter, 11 were considered retrobulbar because of the presence of proptosis, and I was intraocular, involving the choroid. Of the bilateral lesions, the same site was involved in each eye; 6 patients had involvement of the conjunctiva and I retrobulbar involvement.

#### TREATMENT

The initial therapy in 30 patients consisted of irradiation, while 3 patients were treated with surgery alone. In those patients receiving irradiation, surgery was usually limited to an open biopsy, although 2 patients with extensive orbital disease did undergo enucleation as part of their initial therapy.

In all the patients treated with radiotherapy, 280 kv. orthovoltage was selected except in 1 of the patients who had undergone enucleation and was treated with cobalt 60 teletherapy. A beam quality of 1.25 mm. Cu half value layer was predominantly employed. With this modality the cornea and lens could be more readily protected than with supervoltage irradiation. The ports were anterior and/or lateral with selection depending upon the location of the tumor. Usually for lesions limited to the anterior orbit a single anterior port was used, while those with retrobulbar involvement were usually treated with both anterior and lateral ports (Fig. 1). The anterior margin of the lateral port nearly always

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<sup>†</sup> Trainee supported by USPHS Grant No. T1 CA 5181-03 of the National Institutes of Health.

TABLE I

Lymphosarcoma, lymphocytic cell type (LSA)	23
Lymphosarcoma, reticulum cell type (RCS)	6
Lymphosarcoma, mixed cell, reticulum cell	
and lymphocytic cell (mixed LSA and	
RCS) type	2
Benign lymphoma	2
Total	33

extended to the external bony canthus and the beam was angled 5 to 10° posteriorly; *i.e.*, away from the face. With this arrangement the lens of both the treated and of the opposite eye could be avoided, despite the divergence of the roentgen-ray beam. When treating anteriorly, a 3 mm. thick lead shield for the lens and cornea was used. If the lymphoma involved the lid, an internal (corneal) shield was used, while in bulbar and intraorbital lesions, a small, 1–1.5 cm. in diameter, external eye shield placed on the lid was often more suitable.

The tumor dose in this series varied from 5,052 rads in 28 days, in a single case in which the diagnosis was uncertain and the possibilities included undifferentiated carcinoma, to 1,200 rads (air dose) for a patient treated in 1941. The most frequently employed tumor dose, especially in the

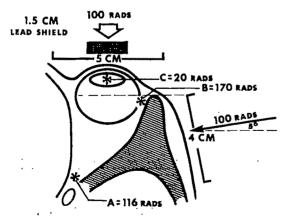


Fig. 1. Anterior and lateral fields. Soft tissue doses resulting from 100 rads given dose to each field. No corrections made for tissue inhomogeneity or obliquity.

TABLE II

TOTAL TUMOR DOSE OF INITIAL TREATMENT
(Usually standard fractionation, daily treatments)

Tumor Dose	No. of Patients
2,0∞ rads or less	8
2,000 to 3,000 rads	10
3,000 rads	9
3,500 rads	2
5, 052 rads	I
Total	30

more recent patients, has been 3,000 rads in 3 weeks (Table II) delivered 5 times per week for lymphosarcoma, lymphocytic cell type. In reticulum cell type the dose has often been 3,500 rads in 3 weeks. The tumor dose was calculated at the greatest depth involved with tumor. With uncompensated anterior and lateral fields there was inhomogeneity, but with the doses and volumes employed this was considered acceptable. The field size usually measured 4-5 cm. in diameter to include the entire orbital contents.

# RESULTS

Twenty-seven of 33 patients had no evidence of local recurrence from 1 to 28 years after treatment (Table III). Four of the patients with recurrence were treated initially with radiotherapy and 2 with surgery.

Of the cases with recurrence following radiotherapy, the histology was lymphosarcoma, lymphocytic cell type in 3 and in the remaining case was lymphosarcoma, reticulum cell type. Two of these patients had disease limited to the retrobulbar area and were treated with a lateral port alone. Recurrence in these 2 cases was anterior, outside the geometric edge of the beam, 17 months and 10 years after therapy. The third patient had bilateral bulbar conjunctival involvement and recurrence in the conjunctiva 8 months later. This patient was treated with lateral and anterior ports, and, in retrospect, received a relatively low dose anteriorly, approximately 1,200 rads. The fourth patient had recurrence in the

Post Initial Therapy (yr.)	Patients at Risk*	Local Recurrence	Generalization	Lymphoma Deaths†
O-I	30	1	6	I
1-2	29	I	I	I
2-4	21		I	49,000
4-6	15	Madestrate	1	
6-11	12	2		
11-16	5	generalised		999 000
16-28	3	sandy shared	***************************************	
	and the same of th	and the same	pascocode	and contracts
Total		41	Q	2

Table III
RESULTS OF RADIOTHERAPY IN 30 PATIENTS

\* Risk of dying at beginning of interval.

† Four other deaths thought not due to lymphoma 3, 7, 12, 20 years after initial therapy.

lower lid after treatment of a tumor in the lacrimal fossa region with the lower lid shielded during therapy. All 4 recurrences were located anteriorly. In the 3 cases where a recurrence was in an area not previously involved with disease, the estimated dose at these sites was 250-600 rads. In the I case where recurrence occurred in an area with clinically evident disease at the time of initial radiation, the dose to this region was approximately 1,200 rads. By contrast in 26 cases treated with radiotherapy without recurrence only 3 patients received a dose anteriorly of less than 1,000 rads. All 4 recurrences which followed radiotherapy were locally controlled after retreatment with irradiation, but 2 developed generalized disease.

Two of the 3 patients treated with surgery alone developed a recurrence. One developed a recurrent lid mass 18 months after initial surgery. This was re-excised and the patient had no evidence of disease for the next 16 years. Another patient developed a recurrence 1 year after excision and was successfully retreated with irradiation. The third patient had a benign lymphoma excised  $5\frac{1}{2}$  years ago and has had no evidence of disease since then.

Nine patients developed generalized disease several months to  $2\frac{1}{2}$  years after treat-

ment of the orbital tumor (Table IV). One of these had a hard mass on the forehead at the time of treatment of the orbit and this in retrospect represented an additional focus of disease. Two of these 9 were quite ill shortly after completing treatment, suggesting that the disease was probably more advanced than originally suspected. Three others developed generalized disease in less than I year after treatment. Two patients have died of lymphoma from generalization, I has been lost to follow-up, while 6 are still alive.

In the group of 24 patients whose disease did not generalize, 3 patients died 3, 7 and 20 years after therapy of unknown cause and a fourth patient died of ovarian carcinoma 12 years after radiotherapy. All 4 of these patients had no eye symptoms at the time of death.

Most patients whose disease was controlled had no residual eye symptoms. Three patients developed cataracts. One had the cataract removed, while the other 2 had vision in the treated eye of 20/25 and 20/200. In 2 exophthalmos remains, probably because of retroorbital scar tissue. There is 1 with persistent epiphora and another with diplopia on downward gaze. Finally, there is 1 who had a retroorbital tumor and papillitis, and whose vision in

<sup>‡</sup> All were subsequently controlled with additional treatment; 2 of the 3 patients treated with surgery also developed local recurrence and are not included in this table.

Table IV

NINE PATIENTS DEVELOPING GENERALIZED DISEASE

Age and Sex	Location of Primary Tumor	Histology of Eye Lesion†		First Manifestation of Generalization	Total Years of Follow-up	Present Status
53M	Retrobulbar	RCS	+	Lytic rib lesions	911	No overt disease
33M	Intraorbital (L)	RCS	+	Jugulodigastric lymph node (L)	113	Died of disease
74F	Retrobulbar	RCS	+	Submandibular and supraclavicular lymph nodes (L and R)	012	Died of disease
59F	Retrobulbar (R)	RCS	+	Liver enlarged	11/2 41/2	Lost to follow-up
43F	Conjunctiva (bi- lateral)	LSA	*	Spleen enlarged	4172	Free of local disease for 2½ years; on mainte- nance dose of cytoxan
34M	Conjunctive and lid (R)	Mixed	+	Jugulodigastric and inguinal lymph nodes (R)	8	Doing well after chemo- therapy and radiother- apy
38F	Lacrimal fossa (L)	LSA	*	Inguinal lymph nodes (L)	9172	No overt disease after chemotherapy and ra- diotherapy
45F	Conjunctiva (L)	LSA	+	Nodule of temporal area (R)	28	Only manifestation of disease is hemolytic ane- mia well controlled with decadron
78F	Intraorbital and lid (L)	Mixed	+	Jugulodigastric, ingui- nal and retroperi- toneal lymph nodes (L)	4 <u>13</u>	No overt disease except for 2×1×1 cm. jugulo- digastric lymph node (R)
Mean age 46						(K)

\* Local control was subsequently achieved with additional courses of radiotherapy.

† Abbreviations as given in Table 1.

the affected eye was limited to finger counting prior to radiotherapy and it has remained unchanged since then.

#### DISCUSSION

An analysis of the AFIP data of Forrest<sup>6</sup> indicates that lymphomas are among the most common malignant intraorbital, extraocular tumors. Turner and Howell<sup>12</sup> cited two series with 22 lymphomas of 216 orbital tumors (10 per cent), and 12 lymphomas of 88 orbital tumors (14 per cent).

The lymphoid tumors of the orbit present considerable diagnostic difficulty for the pathologist. Zimmerman<sup>13</sup> has stated, "Of all the neoplasms and pseudoneoplastic tumors involving the eye and adnexa, I believe no group gives the pathologist more diagnostic and prognostic trouble than the lymphomatous lesions . . ." Turner and Howell<sup>12</sup> stated that there is considerable lack of agreement among skilled observers concerning terminology of cell type, specific diagnostic names, and degree of malig-

nancy. Reese<sup>10</sup> cautions that there is a trend in general pathology to interpret some lesions formerly considered malignant as reactive hyperplasia or indeterminate.

Zimmerman<sup>18</sup> discusses 3 main categories based on the clinicopathologic picture. First are those lesions that are obviously malignant. He states that it is rare to see this type in an adult, presenting first as an orbital lymphoma. The second category is inflammatory non-neoplastic pseudotumors which are sufficiently cellular to give a superficial resemblance to malignant lymphoma, yet have a mixture of other inflammatory cells. The third presents the most difficult problem. The lesions are composed entirely of rather mature lymphocytes, which lack the cytologic features of the obviously malignant lymphoma.

The basic histologic types in our series are given in Table 1. However, in 9 instances there was controversy concerning the pathologic diagnosis. In 7 of these there was a question of whether the lesion was malig-

nant or benign. Six were finally considered to be malignant and I benign. In 2 of 9 there was a question of lymphocytic versus a reticulum cell type of lymphosarcoma. Both of these were finally considered to be lymphocytic cell in type.

Lymphomas may occur in the lids, conjunctiva, lacrimal glands, posterior orbit, or intraocularly. In our series prognosis did not seem to vary with location. There was only I instance of intraocular disease. This agrees with the rare occurrence of intraocular lesions reported in the literature. Reese<sup>10</sup> had 8 intraocular tumors in 171 cases of malignant lymphoma of the orbit. McGavic<sup>8</sup> had I intraocular tumor among 21 cases of malignant lymphoma of the orbit.

The lesions may be bilateral. In our series 7 lesions were bilateral at the time of treatment, 6 of these being conjunctival. Three other cases eventually developed disease in the opposite eye; 2 of these occurred after the disease had spread to other regions of the body. Ahlström et al.,1 reported 3 of 9 with bilateral involvement, but in 2 of 3 the involvement of the other eye occurred 5 and 7 years later and was not proved by biopsy. Turner and Howell<sup>12</sup> reported bilateral involvement in 3 of 4 with primary disease, 1 of 3 with lid involvement, and 2 of 3 with subconjunctival involvement. Lederman<sup>13</sup> feels that the prognosis is worse with initial bilateral involvement. In our cases with bilateral involvement, 5 had no recurrence, and 2 had local recurrence. One of these later developed generalized disease.

The lesions are usually painless and slow-growing. They may cause proptosis or present as a mass lesion. The conjunctival lesions have a grayish-pink or salmon color, a smooth overlying conjunctiva, and a rather sharply demarcated border (Fig. 2). If intraocular, the patient may present with eye pain, blurred or decreased vision. Lymphoma of the lids usually appears as an ill defined nodular mass or masses, with the skin movable over the mass. <sup>12</sup> In our series <sup>11</sup> presented with proptosis. Those with

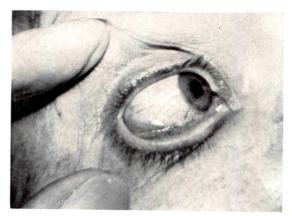


Fig. 2. Lymphosarcoma, reticulum cell type, of bulbar and lid conjunctiva.

conjunctival lesions often initially had irritation of the eye. The patient with intraocular disease presented with decreasing vision.

In several studies the incidence of patients with primary eye lesions developing generalized disease was not stated; however, such an occurrence was reported in 7 of o by Ahlström et al.1 at 1 to 10 years after treatment of the primary tumor, o of 4 by Turner and Howell<sup>12</sup> at 3 to 12 years after treatment, and at least 8 of 40 treated by Lederman.<sup>13</sup> Turner and Howell<sup>12</sup> believe that the patient with primary orbital lymphoma should undergo continued observation for systemic disease because of the rarity of the benign, primary ocular disease. In our series, 9 patients developed generalized disease, 6 of these within I year after treatment of the orbital lesion (Table III). The early occurrence of generalization emphasizes the importance of a complete diagnostic evaluation. The mean age of the patients whose disease became generalized was 46 years, 9 years less than that of the total group, which supports Reese's10 statement that prognosis of orbital lymphoma improves with age.

Of the 9 cases that became generalized, 4 were reticulum cell type and 2 mixed cell type, while only 8 of 33 total patients had the reticulum or mixed cell type. This suggests that the reticulum or mixed cell type is more likely to be, or to become generalnode involvement as one of the first manifestations of generalization. Although the series is too small for a definitive statement, this raises the question of whether the treatment area should include the neck in the reticulum cell type when thorough work-up has not revealed evidence of disease elsewhere.

Many authorities<sup>6,9,10</sup> have indicated that conjunctival lesions have a better prognosis than those in other sites of the orbit. On this point our results are quite inconclusive. Three of our 9 patients who developed generalized disease had conjunctival lesions, a ratio similar to that of the entire group. In 2 of these patients the duration of orbital disease was unusually long, which may have been a factor leading to generalization. One patient previously mentioned received only 1,200 rads to bilateral conjunctival lesions. Over the next 2 years she developed several recurrences and finally manifested generalized disease  $2\frac{1}{2}$  years after her initial therapy. A second patient had a 6 year history of "vernal catarrh" prior to his initial evaluation and treatment at this institution. Fourteen months later extraorbital spread of disease was evident.

The initial presentation in several of the cases that generalized was unusual. One patient had bony erosion on orbital roent-genograms while another patient had pain, a rare symptom for orbital lymphoma. Two other patients had rapidly progressive exophthalmos, of 1 week and 3 months' duration, suggesting virulent disease at presentation.

Irradiation is generally considered the treatment of choice. 9,10,12 Reese<sup>10</sup> believes that surgical intervention is usually indicated only to establish the diagnosis. He advises postoperative irradiation if surgical excision is performed.

There are few reports in the literature concerning the incidence of local recurrence following therapy. Ahlström *et al.*<sup>1</sup> had one local recurrence in 9 patients followed for 1 to 10 years, treated primarily with radiotherapy.

In our series 3 of 4 local recurrences oc-

curred anteriorly in an area not previously involved or treated, and the fourth recurrence was also anterior in a region that received an unusually low dose for clinically evident disease. This suggests that the anterior orbit should receive a significant dose even when not involved with clinically evident disease.

The current treatment plan at this institution is: (1) For bulbar conjunctiva or lid, 3,000 rads at 1 cm. depth is given by an anterior port alone. (2) For more posterior lesions 3,000 rads is given to a depth of 4 cm. by anterior and lateral ports, weighed according to the location of the tumor within the orbit. When the diagnosis is reticulum cell sarcoma, the tumor dose is raised to 3,500-4,000 rads in 3-4 weeks. With the use of orthovoltage the lens and cornea can usually be effectively shielded. This shielding apparently has not resulted in any recurrences, although in the occasional case where the bulbar conjunctiva is involved with tumor near the limbus, the shield has not been employed for the first part of the treatment. With the posterior lesions supervoltage radiation and/or wedge filter may be employed for the lateral field in an effort to lower the dose to bone, especially in the vicinity of Point B in Figure 1.

## SUMMARY

Thirty-three patients with primary lymphoma of the orbit were treated. Thirty had radiotherapy, and 3 had surgery alone as initial treatment. Local recurrence occurred in 5 and in each case was successfully retreated. The recurrences were anterior in low dosage areas, which has resulted in the protocol outlined in the preceding Discussion. Nine developed generalized disease, usually within 1 year after treatment. Two of these patients have died of lymphoma. It appeared that the patients with reticulum cell or mixed cell type lesions were more prone to generalized disease.

The results indicate that local control can be obtained, and that in a significant percentage of patients the disease does not generalize. Even in those who developed ized. Four of the 9 developed neck lymph generalized disease, the eye symptoms were controlled. Complications of treatment were few utilizing orthovoltage technique which facilitates adequate shielding of the lens and cornea.

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# UNUSUAL RADIATION RESPONSE IN VARIOUS INOPERABLE RADIORESISTANT TUMORS\*

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IN SELECTING a topic for this presentation I have intentionally avoided the well trodden path of routine radiotherapy, since a discussion of the treatment of radiosensitive conditions may bring new and interesting statistical information to radiotherapists, but is hardly exciting news for colleagues who devote most of their time to diagnostic work and consider radiotherapy as an interesting although somewhat distant subspecialty.

I have therefore tried to bring something out of the ordinary, and the result of my endeavor is this short report describing the case histories, treatment approach and results in a number of patients who were unusual for 2 reasons: (I) they were suffering from rare tumors; and (2) more than half showed gratifying and remarkable response to the treatment with irradiation, to which, according to the literature, they were supposed to respond only sporadically.

# MATERIAL

There were 16 such patients to be evaluated (Table I): 4 gastric carcinomas, 7 soft tissue sarcomas, 2 osteogenic sarcomas, I reticulum cell sarcoma with involvement of the entire bony skull, I cylindroma and I glomus jugulare tumor, the diagnoses of which have been documented by microscopic examination. None of these patients had shown evidence of generalized metastases.

I should like to emphasize that the treatment of choice for these pathologic entities is surgery and that these specific cases were treated with irradiation only because the extent of the disease or its location, or both, made a successful surgical procedure impossible.

### GASTRIC CARCINOMA

Four patients with gastric carcinoma are shown in Table 1. In 2 of these patients the disease was classified as clinically inoperable, while the other 2 developed local recurrence after previous surgical removal of the tumors; there was no evidence of generalized disease in any of these patients. All 4 patients were treated with a tumor dose of 4,000 to 5,000 rads given in 4-5 weeks time with a 2 MV. roentgenray unit. All of the patients showed symptomatic relief and tolerated their treatment extremely well, although there was quite a difference in the individual reaction with regard to an extended beneficial effect of the treatment.

Two patients have shown a surprisingly long survival. The first had developed recurrent abdominal disease 2 months after surgery for a large carcinoma of the stomach, while the second patient was inoperable at the time of an exploratory laparotomy because the disease extended into the liver and pancreas. Both patients were able to return to their normal active life. Their improvement began during therapy and lasted as long as we were able to follow them, namely  $2\frac{1}{2}$  years.

The other 2 patients, one after previous gastric surgery, the other treated only by irradiation, died 11 months and 9 months, respectively, after treatment, but even they enjoyed positive palliation with a number of good months free of complaints.

<sup>\*</sup> Presented at the Seventy-first Annual Meeting of the American Roentgen Ray Society, Miami Beach, Florida, September 29-October 2, 1970.

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Table I
TOTAL NUMBER OF PATIENTS: 16

Diagnosis	No. of Patients
Gastric carcinoma	4
Liposarcoma	4
Fibrosarcoma	3
Osteogenic sarcoma	2
Reticulum cell sarcoma	I
Cylindroma	I
Glomus jugulare tumor	I

#### SOFT TISSUE SARCOMAS

The second patient group suffered from soft tissue sarcomas; *i.e.*, liposarcomas and fibrosarcomas. The treatment of choice of these diseases is adequate surgical removal, and radiotherapy should not be considered as an alternative to surgery.

### LIPOSARCOMA

The 4 patients who were treated for liposarcomas have presented us with the following problems (Table III):

The first patient had an exploratory laparotomy for an enormously large tumor of the upper abdomen which measured  $16\times10\times8$  cm. and was inoperable because of dense invasion of the pancreas. No attempt was made to remove the tumor surgically and the patient was referred for treatment to the Radiotherapy Department. He received a tumor dose of 5,000 rads which was given in 5 weeks time through 2 large opposing fields on a 2 MV. roentgen-ray unit. The patient tolerated the treatment extremely well and has been alive, asymptomatic and without evidence of disease now for 17 years.

The second patient had a large liposarcoma measuring  $8\times10$  cm. overlying the scapula. It was surgically removed but the patient was referred for postoperative irradiation because tumor implants were left behind in the trapezius muscle. A tumor dose of 5,000 rads was given through a 15×15 cm. field in 5 weeks time on the 2 MV. roentgen-ray unit and the patient

TABLE II

CARCINOMA OF THE STOMACH
TOTAL NUMBER OF PATIENTS: 4

	No. of	Surviva	ıl Time
	Patients	Alive	Dead
Treated for recurrent disease after	I		2½ yr.
surgery	I		II mo.
Total	2		
Treated for inoperable	Į.	g gympagagagan menn dibadassan lan fa fil di sili 1999 (1994) di 1997 (1994) di 1	29 mo.
disease	I		9 mo.
Total	2		

has remained free of disease and without complaints for 9 years.

It was interesting and gratifying to watch over the years the excellent radiation response in these 2 patients, which was far beyond expectation.

The third patient gave us some insight into body reaction which we have observed for a long time in other fields of radiotherapy, especially in breast and lung pathology; i.e., that previous surgery which is not able to remove the entire malignant tumor, but cuts through it, impairs the effect of radiotherapy. This patient had an amputation of the leg for a primary liposarcoma and developed I year later various metastases, some of which had been removed by a conservative surgical procedure, which had been obviously incomplete because they recurred immediately, while others had remained untouched. When this patient was referred for radiotherapy, the various metastatic lesions had approximately the same size. They were all treated with the same dosage, but the radiation response was a different one. The sites where disease had been cut through at the time of an attempted removal had the least favorable response to therapy and needed a higher dosage to remain controlled.

TABLE III

LIPOSARCOMA

TOTAL NUMBER OF PATIENTS: 4

	No. of	Surviva	l Time
	Patients	Alive	Dead
Treated without previous	I	17 yr.	
surgery	1		1½ yr.
Total	2		
Treated after	I	9 yr.	
surgery	r	ı yr.*	
Total	2		

<sup>\*</sup> Six sites treated.

The fourth patient watched a tumor mass on the left thigh for 15 months before he sought medical advice. After biopsies were taken at another hospital and the diagnosis of liposarcoma established, a hemipelvectomy was offered to the patient which he refused, and he was therefore referred for radiotherapy. A tumor dose of 4,100 rads was given in 12 days on the 2 MV. roentgen-ray unit and growth restraint was noted for 11 years. The patient then died of generalized disease. Rare as these cases are, they are not unique. During the past years a few articles have appeared which mentioned limited radioresponse of liposarcomas to megavolt therapy.

# FIBROSARCOMA

Two of the three patients with fibrosarcomas showed decrease of the mass, improvement of pain and general condition (Table IV). The improvement lasted in I patient I year and 6 months. After that time he developed generalized metastases and died I year and 8 months after radiotherapy. A biopsy which had been taken of the tumor area I year after radiotherapy showed "fibrosis and radiation changes only." The other patients died between 6 and I2 months after radio-

Table IV

FIBROSARCOMA

TOTAL NUMBER OF PATIENTS: 3

	No. of	Surviva	d Time
	Patients -	Alive	Dead
Treated after	I		20 mo.
previous	1		6 mo.
surgery	1		10 mo.
	-		
Total	3		

therapy, which had not been able to control the disease.

#### RARE TUMORS

Osteosarcomas are characterized by anaplastic osteoid producing, bone forming malignant connective tissue. The tumor nearly always involves the medullary cavity and extends through the cortex to involve the periosteum, either by elevating or perforating it. Osteosarcoma is one of the most radioresistant tumors which is known to continue to grow even after doses that severely damage associated normal tissues.

Two patients had to be accepted for radiotherapy because of the location of the disease in vertebrae (Table v). The first patient with osteogenic sarcoma of T3, proved by biopsy, had not been treated with previous surgery. He received a total tumor dose of 4,600 rads in  $3\frac{1}{2}$  weeks time and is alive and asymptomatic 12 years after the therapy.

The second patient had a partial laminectomy of T12-L4 performed, but the disease had recurred and he was referred for radiotherapy as further surgery was not possible. A tumor dose of 3,500 rads was delivered in 2 weeks time and the patient's pain subsided but he died of generalized disease 10 months later.

Next, I should like to mention a patient who presented himself with a reticulum cell sarcoma which had involved the entire bony skull and scalp. The patient had

 $T_{ABLE}\ V$  other rare tumors total number of patients: 5

		Survival Time	
Disease	No. of Patients	Alive	Dead
Osteogenic sarcoma			
treated without previous surgery	I	12 yr.	
treated after surgery	I		10 mo.
- '	Agramatical State		
Total	2		
Reticulum cell sarcoma involving the entire bony skull			
treated with irradiation exclusively	1	$1\frac{1}{2}$ yr.	
Cylindroma			
treated after surgery	I	5 yr.	
Glomus jugulare tumor			
treated with irradiation exclusively	1	7 yr.	
•	Actions		
Total	5		

watched the disease for a long time before he asked for medical help and when he finally came, the disease had hopelessly advanced. He was only treated with irradiation and the disease responded extremely well to a combination of low voltage and cobalt 60 irradiation, where a total dose of 5,500 rads was evenly delivered to the involved skull and scalp in 6 weeks time. A dose of 3,200 rads was first given with the cobalt 60 unit and this dose was followed with 2,300 rads with a 100 KV. machine. The tumor disappeared and the patient has remained asymptomatic and well for 18 months.

The cylindroma, which is included in this collection of rarities, affected the ear of the patient. It had been treated surgically but had recurred and represented a serious problem due to severe pain. The patient had become a drug addict because her pain could only be controlled by regular and high doses of morphine. She lost the pain during treatment, morphine could be eliminated and the patient has been free of disease and of her addiction for the last 5 years.

A similar response can be reported in a patient with a glomus jugulare tumor which

had caused destruction of the petrous pyramid and temporal bone and had involved the 8th and 9th cranial nerves. This patient is now without evidence of disease and has remained asymptomatic 7 years after the completion of treatment.

# CONCLUSION

It is the purpose of this paper to demonstrate unexpected radiation responses in various malignant tumors, which have resulted in long lasting survivals: a minimum of 5 years, in 5 of the 16 patients, with 2 of the patients still alive with the potential for longer lasting survivals.

These results are not reported in order to advocate the use of irradiation as a routine procedure or to compete with surgery. They are reported to point out the unpredictability of a number of malignant diseases—a fact which ought to encourage us to offer well planned radiotherapy when surgery is no longer feasible, even in diseases which, according to the literature, do not respond to irradiation.

Of course, we have been unsuccessful in a number of patients who suffered from the discussed malignant tumors. But as no laboratory test or theoretic evaluation today is able to select a responsive case, no patient should be given up as hopeless and left to his fate before our therapeutic armamentarium has been exhausted. This brings me to the last point I would like to make.

This report has shown the effect of irradiation without concomitant chemotherapy. I consider this the proper primary treatment approach in diseases which are: (1) still localized, and (2) for which a specific chemotherapeutic agent is not known. I believe that the addition of unspecific chemotherapy can be harmful by breaking down the host resistance which is of utmost importance and of which we know so little.

Furthermore, it is felt that nothing is lost by reserving chemotherapy for such a time when it has become obvious that radiotherapy has not affected the disease sufficiently, but when the radiation may have stimulated some immunobiologic resources of the body, thus making the disease possibly more receptive for chemotherapy.

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# RESULTS IN TREATMENT OF PURE SEMINOMA OF THE TESTIS\*

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THERE have been numerous reports of series of patients treated with irradiation of the lymphatics after orchiectomy for pure seminoma of the testis. 10-13 In most series, iliac and paraaortic lymphatics were irradiated, but some authors have suggested prophylactic irradiation of the mediastinum and left supraclavicular area. 8-10 Also, the opposite testicle usually has not been irradiated because of the low incidence of involvement, although some have purposely included it in the irradiation field. 7

The purpose of this study is to examine the treatment techniques and to report on the results in a group of patients treated at The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, especially with regard to prophylactic irradiation of the mediastinum and left supraclavicular area. The question of irradiating the remaining testicle also is evaluated.

# MATERIAL

Ninety-six patients with testicular tumors diagnosed as pure seminoma were irradiated postorchiectomy during the period from March 1944 through December 1965. Excluded are patients who received irradiation outside The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, or who were seen only for consultation. Two patients refused treatment and 3 patients had disease considered too advanced for treatment.

These cases were staged according to the

following clinical staging modified from Boden and Gibb:<sup>1</sup>

Stage I. Tumor confined to the testis Stage II. Disease outside of the testis, such as scrotum, spermatic cord, and/or lymphatics up to diaphragm

Stage III<sub>A</sub>. Disease beyond the diaphragm but still confined to the lymphatics; [i.e., mediastinal and/or left supraclavicular disease, or massive retroperitoneal disease

Stage III<sub>B</sub>. Extranodal abdominal disease (visceral) or distant metastases (disseminated)

Physical examination, surgical findings at orchiectomy, and radiographic studies, including lymphangiography in the more recent patients, were used in the clinical staging.

Many of the patients had orchiectomy at other hospitals before coming to the M. D. Anderson Hospital for radiation therapy. However, in all instances, the pathologic material was reviewed by the Department of Pathology at the M. D. Anderson Hospital. All patients had pure seminoma, according to the pathologic classification of Dixon and Moore.<sup>4</sup> Three patients were excluded from this analysis because metastases from other than pure seminoma were found at autopsy.

# TREATMENT TECHNIQUES

After orchiectomy, patients with Stages I, II, and IIIA disease received irradiation only. Patients with disseminated disease

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(Stage III<sub>B</sub>) were treated with palliative irradiation or a combination of chemotherapy and irradiation. In the patients who had orchiectomy at other hospitals, and who did not have a radical orchiectomy with high ligation of the spermatic cord, a portion of the scrotum was included in the radiation field, depending on both extent of operation and physical findings. The remaining testicle was shielded. The inguinallymph nodes were usually included. Typical inguinal-iliac, paraaortic, mediastinal, and left supraclavicular portals are shown in Figure 1.

Patients with Stage I disease generally received 2,000 rads tumor dose in  $2\frac{1}{2}$  weeks to the inguinal-iliac lymph nodes with orthovoltage or 2,500 rads tumor dose in 3 weeks with cobalt 60 teletherapy, assessed 3.0 cm. anterior to the midplane of the pelvis. Similar doses were given to the paraaortic lymph nodes, calculated at midplane. A few patients with Stage I disease also

received elective irradiation to the med astinal and left supraclavicular area tota ing 2,500 rads tumor dose in 3 weeks.

In patients with Stage II disease, the treatment portals generally were the same except that irradiation of the mediastinu and left supraclavicular area was adderoutinely. Usually, bulky involved lymphodes received an additional 500 to 1,000 rads tumor dose through reduced fiel after the basic dose of 2,500 rads. Some patients received total abdominal irradiation with the cobalt 60 moving-strip technique,<sup>2,3</sup> delivering tumor doses of 2,500 rads to each segment of the irradiativolume in 10 to 12 days.

The patients presenting with Stage I disease received radiation therapy according to the extent of the disease. Technique were variable and ranged from palliative irradiation in the advanced cases to mo aggressive techniques in those with pote tially controllable disease (Stage III.

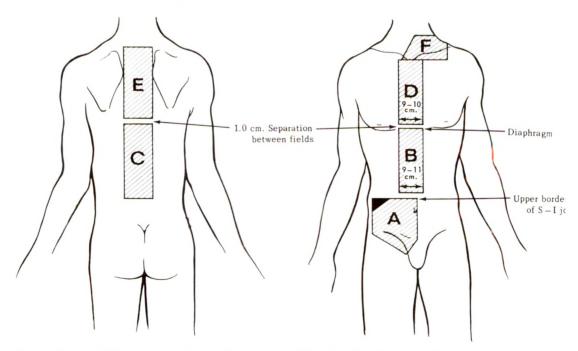


Fig. 1. Typical field arrangement for seminoma managed by cobalt 60 teletherapy. Through field A, 2,500 ra tumor dose in 3 weeks is delivered at a point 3.0 cm. anterior to midplane. Through fields B and C, a tum dose of 2,500 rads in 3 weeks is given at midplane. Portal width in fields B and C depends on lymphangi graphic findings, but is usually 9 to 11 cm. wide. Fields E and D receive 2,500 rads tumor dose in 3 wee midplane; field F receives 2,500 rads given dose in 3 weeks. An additional 1,000 to 1,500 rads may be giv through reduced fields to bulky lymph nodes.

These tumor doses ranged from 2,500 rads in 3 weeks (250 kv.) to 4,000 rads in 5 weeks (cobalt 60). When whole-abdomen cobalt 60 irradiation was used, fields were reduced after 3,000 rads in 4 weeks.

In recent years, all patients have had lymphangiography, although it is known that some testicular lymphatics are not filled by this method.14 These studies are useful in verifying the accuracy of the treatment portals. Sufficient width must be included at the level of the kidneys to ensure that lymph nodes filled directly from testicular lymphatics will be included, particularly on the left. When there are large bulky lymph nodes, very wide fields, on the order of 12 cm. or more, or even total abdomen irradiation is preferred for the first 2,000 to 2,500 rads, taking care that the kidneys do not receive more than 1,500 rads.

# RESULTS

Table I shows the results in patients by clinical stage according to the areas of treatment. Most Stage I patients were treated with inguinal-iliac and paraaortic fields only. A small number had additional treatment to the mediastinum and left supraclavicular area. There is only I instance of recurrent lymph node disease in the abdomen and mediastinum, and this occurred in a patient in whom a second seminoma subsequently developed in the opposite testicle with presumed reseeding of the lymphatics.

In Stage II disease, the failure rate is also very low, with only I patient showing recurrence in the treated lymphatics. A few Stage II patients were irradiated only to the iliac and paraaortic lymph nodes because the disease was considered limited, either within the spermatic cord, or because of a slightly abnormal intravenous pyelogram. Those patients with more extensive lymphatic disease were treated to inguinaliliac and paraaortic areas plus elective irradiation of the mediastinal and supraclavicular areas.

Most patients with Stage III tumors

(Table I) were treated palliatively. However, 4 of 6 patients have no evidence of disease at 36 months or more (Stage III<sub>A</sub>). These are patients who presented with left supraclavicular and/or mediastinal lymphatic disease as well as abdominal disease, and were treated to the iliac, paraaortic, mediastinal, and left supraclavicular areas, often using whole-abdomen irradiation for the first 3,000 rads.

#### COMPLICATIONS

There was I patient death directly related to complication of treatment. This patient developed radiation nephritis after irradiation of the whole abdomen with the cobalt 60 trunk-bridge technique to an estimated midplane tumor dose of 4,800 rads. A second patient was treated with kilovoltage, 2,500 rads in  $3\frac{1}{2}$  weeks, to the inguinaliliac, paraaortic, mediastinal, and left supraclavicular lymphatics and died 17 months later with the diagnosis of acute leukemia. This patient did incur a severe hematologic depression with hypoplastic bone marrow after irradiation. Although this may possibly be classified as a complication of treatment, the relationship between the acute leukemia and the irradiation is not proved. There was one other complication —that of radiation sigmoiditis—following iliac and paraaortic lymphatic cobalt 60 irradiation (2,500 rads in 3 weeks); this was managed successfully by partial sigmoid colectomy.

# DISCUSSION

The results in Stage I disease are in keeping with those reported by other authors.<sup>5,8,9,11</sup> Ninety-five per cent of the patients show no evidence of disease at 36 months, this is considered valid for analysis of treatment techniques since almost all failures occur before 36 months. Because lymphadenectomy series have shown regional (iliac and paraaortic) lymph node metastases in 10 to 19 per cent of patients with Stage I disease,<sup>6,9,11,12</sup> irradiation of the iliac and paraaortic lymph nodes is justified. Since the only failures in this

TABLE I

STATUS OF PATIENTS IN TREATMENT GROUP NO EVIDENCE OF DISEASE 36 MONTHS OR MORE (March 1944 through December 1965)

	(March 1944		1							
	Areas	Areas Treated								
Stage and Number of Patients	Iliac Paraaortic	Iliac, Paraaortic,† Mediastinal and Left Supraclavicular Area	of Radia- tion Therapy (Palliative)	dence of Disease 36 Months or More						
I (58)	1 Dead distant metastases 11 months 1 Second primary, opposite testicle, 36 months recurrence abdomen, mediastinum	6/7 1 Acute leukemia, hypoplastic marrow, 17 months		55/58 95 per cent						
11 (21)	6/7* 1 Lost to follow-up, 2 months	12/14† 1 Dead 11 months, lymph nodes+distant metastases 1 Radiation nephritis		18/21 86 per cen						
Ш <sub>А</sub> (-6)		4/6 1 Uncertain 1 Lymph node involvement		4/6						
Шв (11)			1/11‡	1/11						

\* Limited to spermatic cord or minimal lymph node disease.

† More advanced regional lymph node disease.

‡ Disseminated disease.

group were from a second testicular primary (or metastasis) and from distant metastases, there is a lack of supporting evidence for irradiating electively the mediastinum and left supraclavicular areas in patients with Stage I seminoma.

Two patients in the group of 96 who received radiation therapy were noted to have bilateral testicular seminoma (whether metastasis or a new primary is not known). One patient was referred after having had previous orchiectomy and then a second orchiectomy 3 years later for the contralateral tumor. He received irradiation of the contralateral iliac and paraaortic lymph nodes in the amount of 2,500 rads and is without evidence of disease after 56 months.

The second patient developed a contralateral tumor 36 months post-treatment

and succumbed 5 years post-treatment from disseminated lymphatic disease and pulmonary metastases. At the time of the second tumor, retreatment of the abdominal lymphatics was not done because of previous irradiation. It is postulated that reseeding of the lymphatics occurred at that time.

Therefore, the incidence of bilateral testicular seminoma in our material is 2.5 per cent. This is not high enough to warrant prophylactic irradiation of the remaining testicle and is in keeping with that reported by other authors.<sup>11–13</sup>

#### CONCLUSIONS

1. Irradiation of the iliac and paraaortic lymphatics to the dose of 2,500 rads appears sufficient for Stage 1 seminoma. Elective

irradiation of the mediastinum and left supraclavicular area is not indicated.

- 2. For patients with Stage II disease, we suggest irradiating the iliac and paraaortic lymphatics followed by the mediastinum and left supraclavicular area.
- 3. Aggressive treatment of Stage III<sub>A</sub> patients will result in control of the disease in most patients.
- 4. There is no indication for irradiating the opposite testicle, since the incidence of bilateral testicular seminoma or metastasis to the other testicle is quite low.

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## ROENTGENOLOGIC FEATURES OF PULMONARY CARCINOMATOSIS FROM CARCINOMA OF THE PROSTATE\*

By DAVID A. LEGGE, M.B., D.M.R.D., C. ALLEN GOOD, M.D., and JURGEN LUDWIG, M.D. ROCHESTER, MINNESOTA

METASTATIC carcinoma of the lungs usually presents roentgenographically as single or multiple discrete nodules. Occasionally, the tumor spreads through the pulmonary lymphatic vessels and may present as a linear interstitial pattern. Although seldom diagnosed clinically, metastatic deposits in pulmonary lymphatic vessels not infrequently are found at autopsy in cases of carcinoma of the prostate.2 In some of these cases the lesions are microscopic, but in others they produce apparent, if subtle, changes on the thoracic roentgenogram. Recognition of these roentgenologic changes is essential because they may represent the first manifestation of metastatic spread from carcinoma of the prostate, and because appropriate therapy may result in regression of the metastatic tumor.

The purpose of this paper is to review the roentgenologic findings observed in a series of patients at the Mayo Clinic in whom carcinoma of the prostate produced metastatic growths in and around the pulmonary lymphatic vessels.

#### MATERIAL AND METHOD

All cases of carcinoma of the prostate with autopsy, except those in which the carcinoma was occult, at the Mayo Clinic between January 1965 and April 1970 were reviewed. In the cases in which pulmonary metastases were found, the gross and microscopic findings were re-examined and correlated with the thoracic roentgenograms.

#### RESULTS

Sixty-four cases of carcinoma of the prostate were studied, and pulmonary metas-

tases were found in 15. In 3 of these 15 cases, the pulmonary deposits were nodular; in the remaining 12, they were situated in and around the pulmonary lymphatic vessels (Fig. 1, A and B).

In 5 of the 12 cases, roentgenograms of the lungs appeared normal; in 2, pulmonary vascular congestion, atelectasis, and bronchopneumonia were present, which made roentgenologic evaluation of possible metastases unreliable. In 1 additional case, a right-sided pleural effusion was present, and this was shown at autopsy to be due to tumor spread in the subpleural lymphatic vessels.

In the remaining 4 cases, manifestations of the pulmonary metastases were present on the thoracic roentgenograms. In I case, fine horizontal lines (Kerley B lines) were seen near the right and left costophrenic angles (Fig. 2, A and B). The patient had had a pathologic rib fracture and this was the first manifestation of metastasis; other skeletal metastases did not become apparent until after the septal lines were found on the thoracic roentgenogram. This patient had no dyspnea or other respiratory symptoms. In the second case, the thoracic roentgenogram also showed horizontal lines in the right and left costophrenic angles, and these were associated with a bilateral pleural effusion (Fig. 3, A-C); these findings were present before roentgenologic evidence of bone metastases. Dyspnea developed when the pleural effusion increased. In the third and fourth cases, the pulmonary metastatic lesions were more advanced and thoracic roentgenograms revealed a coarser linear interstitial pattern that diffusely involved both lungs (Fig. 4, A and B;

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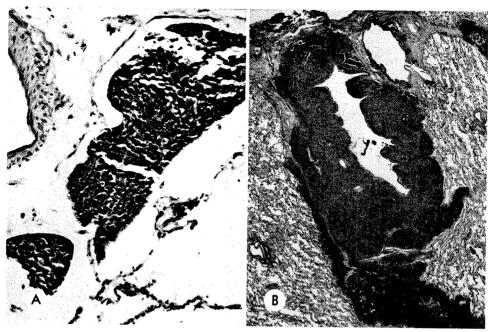


Fig. 1. (A) Distended periarterial pulmonary lymphatic vessels with metastatic adenocarcinoma in lumen in a 76 year old man. Adenocarcinoma of the prostate was diagnosed 17 months prior to death. (Hematoxylin and eosin; ×135.) (B) Peribronchial cuffing by metastatic carcinoma, probably secondary to carcinomatous lymphangiosis, in a 72 year old man. Adenocarcinoma of the prostate was diagnosed 8 years prior to death. (Hematoxylin and eosin; ×10.)

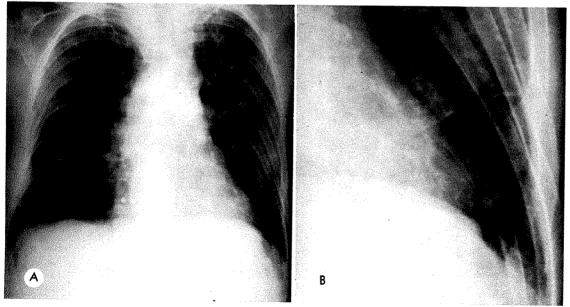
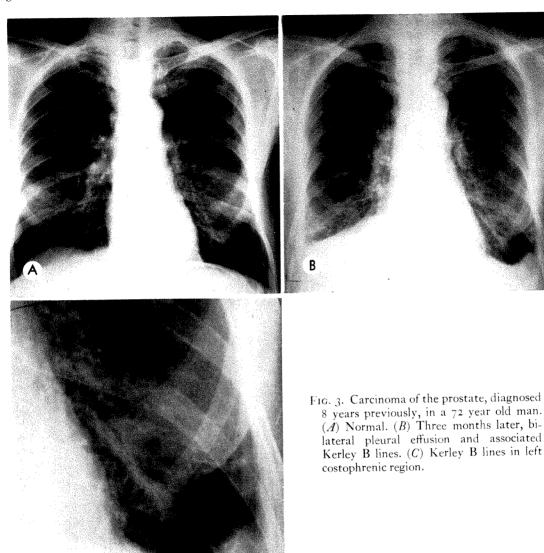


Fig. 2. Carcinoma of the prostate, diagnosed 7 years previously, in a 70 year old man. (A) Pathologic fracture of the right seventh rib later proved to be due to tumor metastasis. (B) Kerley B lines are best seen in left costophrenic region.

C



and 5, A and B). These 2 patients had cough and dyspnea. In 1 case, roentgenologic evidence of spinal metastasis had been noted 2 months before the findings on the thoracic roentgenogram; in the other, pulmonary metastases were apparent before bone metastases could be diagnosed roentgenologically.

#### DISCUSSION

Tumor spread in the pulmonary lymph vessels has long been known to pathol-

ogists, but the roentgenologic features received little attention prior to Trapnell's report. According to this author, nodular or diffuse opacities may be present on the roentgenograms when carcinomatosis involves pulmonary lymphatic vessels. However, the most characteristic findings are fine linear densities which either point toward the hilum (A lines) or are perpendicular to the pleural surface (B lines). These changes may be associated with hilar lymph node enlargement or with pleural effusion.

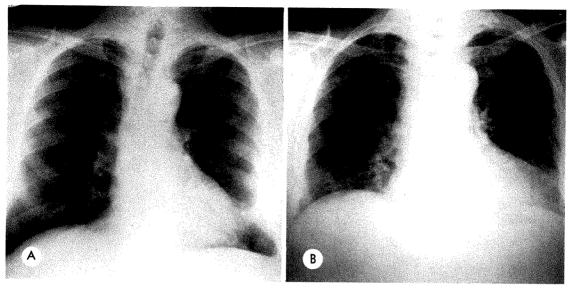


Fig. 4. Carcinoma of the prostate, diagnosed 18 months previously, in a 71 year old man. (A) Normal. (B) Fourteen months later, showing coarse linear interstitial pattern diffusely involving both lungs. There are associated multiple small nodules.

The pulmonary lymphatic vessels are small, even when distended, and so alone are unlikely to account for these changes. However, as intravascular growth increases, tumor cells may infiltrate the adjacent lung parenchyma. This results in perivascular and peribronchial cuffing by tumor cells, which is probably responsible

for the changes on the thoracic roentgenogram.

Carcinomas arising in the bronchus, stomach, pancreas, or breast are considered to be tumors commonly spreading to the pulmonary lymphatic vessels.<sup>3</sup> In pulmonary carcinomatous lymphangiosis, the prognosis usually is grave.<sup>3</sup> On the other

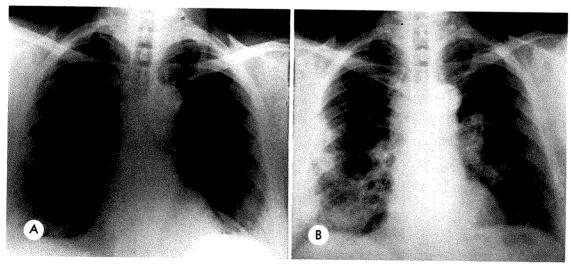


Fig. 5. Carcinoma of the prostate, diagnosed 3 years previously, in a 56 year old man. (A) Diffuse linear interstitial pattern is best seen in the lower lung fields. (B) Two months later, the changes are more advanced.

hand, in carcinoma of the prostate, pulmonary carcinomatous lymphangiosis may be amenable to treatment, and prolonged survival in such cases has been reported by Bolton<sup>1</sup> and Schwartz and associates.<sup>4</sup> Thus, in carcinoma of the prostate, the roentgenologic demonstration of pulmonary carcinomatous lymphangiosis is of considerable importance, especially since this may be detected roentgenologically before metastatic bone lesions are apparent. Unfortunately, this study revealed that metastatic infiltrates in and around pulmonary lymphatic vessels often were too small for roentgenologic detection. Nevertheless, this should not deter the radiologist from searching for these pulmonary changes in every case of carcinoma of the prostate. The presence of typical linear densities on a thoracic roentgenogram suggests pulmonary carcinomatous lymphangiosis, even in the absence of a known primary tumor, providing there is no evidence of left heart failure or pneumoconiosis.

#### SUMMARY

Sixty-four cases of carcinoma of the prostate studied at autopsy were reviewed. In

12, metastases involved pulmonary ly phatic vessels, and, in 4 of these 12, a lir interstitial pattern on the thoracic roc genogram represented pulmonary carcimatosis involving lymphatic vessels perilymphatic tissue. These roentgenolo findings may be the first manifestation metastatic spread from a carcinoma of prostate. Early recognition may per effective therapy.

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## BONE METASTASES IN CANCER OF THE ESOPHAGUS\*

By JOHN T. GOODNER, M.D.,† and A. D. M. TURNBULL, M.D.‡

THE spread of esophageal cancer by invasion of adjacent tissues, metastases to regional lymph nodes, and hematogeneous dissemination has been well documented. The literature dealing with the incidence and mechanism of blood-born metastases to bone from tumors with a known predilection to do so is also extensive. There is, however, little information regarding the frequency of osseous involvement by carcinoma of the esophagus, and the few available reports suggest an incidence of 7 to 9 per cent.<sup>1,2,4</sup>

A review of 1,909 cases of esophageal cancer seen at Memorial Hospital between 1928 and 1968 provided 100 patients in whom metastatic involvement of one or more bones was present, an incidence of 5.2 per cent.

This report presents a detailed analysis of these patients with particular reference to the site and histologic type of the primary tumor, the bones involved, and the results of treatment.

#### CLINICAL MATERIAL

Sex. There were 83 males and 17 females with a ratio of approximately 5:1.

Age. The majority of patients were between 40 and 60 years of age. The oldest male was 82 and the oldest female was 69, the females tending on the average to be 10 years younger than the males (Table 1).

Site of primary tumor. There were 5 patients with tumors in the cervical esophagus, 21 in the upper thoracic esophagus, 57 in the midthoracic esophagus, and 17 in the distal thoracic esophagus (Table II).

Pathology. Epidermoid or squamous cell carcinoma was the most frequent histologic type<sup>3</sup> in the total series, and was seen in 89

of the 100 patients in this study. Primary adenocarcinoma was found in 6 patients while 3 had anaplastic or unclassified carcinoma. In 2 patients the primary lesion was not biopsied (Table III).

Location of metastases. Lesions in one or more ribs or vertebrae were considered as a single area of involvement, and 75 patients were included in this category. Two separate sites of metastases were seen in 13 patients, 3 separate sites in 6 patients, 4 sites in 4 patients and 5 in 2 patients (Table IV). Thus, in the 100 cases, there were 145 different bones involved in one combination or another. Figure 1 demonstrates the incidence of the various bones involved.

Method of diagnosis. There was autopsy confirmation in 21 patients and biopsy of the metastases in 2 patients. Of the remainder, a roentgenographic diagnosis was relied upon in 54 patients, while in 23 cases the diagnosis was based on strong clinical evidence only.

Treatment of the primary tumor. Radiation therapy was used in 63 patients, and surgery in 21 patients. These 2 modalities were combined in 6 patients, while 10 received no treatment to their primary lesion (Table v).

#### RESULTS

Thirty-nine of the 100 patients received irradiation to their metastases, of whom 26 had a single area of involvement. Sixty-one patients were not treated. The 13 patients with multiple areas of metastases received treatment to a single area only; *i.e.*, I patient had skull, rib, vertebrae, scapula and femoral involvement with treatment given only to the vertebrae. Another, with biopsy-

1-5, 1970.
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<sup>\*</sup> Presented at the Fifty-second Annual Meeting of the American Radium Society, Coronado Island, San Diego, California, March

No. of Ca:

89 6

3

2

100

Table I

Table III
PATHOLOGY

Pathology

Epidermoid or squamous cell

carcinoma

No biopsy

Total

Adenocarcinoma Anaplastic or unclassified

Age (yr.)	No. of Cases
40-49	14
50-59	39
60–69	37
7 <b>0</b> –79	8
80–89	2
	ago di anno ago de
Total	100
Variation in tota Variation in mal Variation in fem	es 42-82

proven metastasis to the proximal phalanx of the left 5th finger which was treated with irradiation, later developed metastases to ribs and skull which were not treated.

Seven patients whose primary lesion was treated with irradiation only, survived 12 to 18 days following treatment of the metastasis. The average survival time following treatment of the primary lesion in 5 of these patients was 1.8 months. Of the 2 patients in this subgroup, I received no treatment to the primary lesion and I survived only 16 days after its initiation.

Of the remaining 32 cases, there were 9 patients of whom 1 with multiple metastases was treated. In this subgroup, the average survival time was 3 months following treatment of the primary lesion and 1.5 months following treatment of the metastases.

The average survival time following treatment of the primary lesion in the 23 patients in whom a single area of involve-

TABLE II
SITE OF PRIMARY LESION

Site	No. of Cases
Cervical	5
Upper thoracic	21
Midthoracic	57
Distal thoracic	17
Total	100

ment by metastasis was treated was months but only 3.1 months follows treatment of the metastases.

#### DISCUSSION

It is apparent from this review of 1,6 patients with carcinoma of the esophas that osseous metastases are an uncomm and late manifestation in the course of t disease. The incidence of 5.2 per cent slightly less than the 8 per cent figure ported by Dormanns in his review of 1,4 patients.<sup>2</sup>

No apparent relationship was noted tween the site or treatment of the primalesion, and the occurrence and distribut of bone metastases. The predominance single areas of metastases may be due the fact that survival following their accovery was rarely more than 3 months gardless of further treatment.

The predominance of metastases in bones of the trunk may reflect the int

TABLE IV
NUMBER OF METASTASES

Metastases	No. of Cases	No. of Metastas		
Single Double Triple Quadruple Quintuple*	75 13 6 4 2	75 26 18 16		
Total	100	145		

\* Skull, vertebrae, rib, scapula, femur.

\* Navicular, capitate, cuneiform, metataraus and vertebra.

TABLE V
TREATMENT OF PRIMARY LESION

Treatment	No. of Cases
Radiation therapy	63
Surgery	21
Combined	6
None	10
Total	100

connection of venous drainage which may exist between the esophagus, ribs and vertebrae. Furthermore, extensive search of the long bones and pelvis for occult metastases is not a routine part of most autopsy examinations.

No attempt was made to perform skeletal surveys on a routine basis, and most metastases were discovered by follow-up chest roentgenograms or during the investigation of symptoms of pain.

Treatment of these areas which were mainly osteolytic was reserved for those in whom pain was a major symptom or in whom there was impending fracture of a weight-bearing area. Relief of pain occurred in approximately 50 per cent of the patients treated, and the recommended average dose is 1,500 to 2,000 r over 2 to 3 weeks. No statement can be made regarding the possible role of chemotherapy in the treatment of osseous metastases.

It was obvious that radiation therapy to areas of bone involvement did not prolong survival.

#### SUMMARY

- 1. Carcinoma of the esophagus metastasized to the skeletal system late in the course of the disease in 5.2 per cent of 1,909 patients seen at Memorial Cancer Center.
- 2. Radiation therapy in doses of 1,500 to 2,000 r to areas of pain or impending

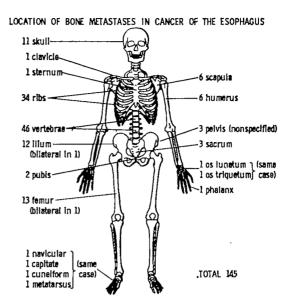


Fig. 1. Incidence of various bones involved in metastases in cancer of the esophagus.

fracture was beneficial in 50 per cent of the patients treated, but unfortunately did not prolong their survival.

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## EXTRA NODAL SPREAD OF HODGKIN'S DISEASE\*

By ANTONIO MEDINA, M.D., D. L. BENNINGHOFF, M.D., and M. R. CAMIEL, M.D. BROOKLYN, NEW YORK

STUDIES<sup>7,9</sup> of the natural history and effects of treatment of Hodgkin's disease have lead to favoring the concept that Hodgkin's disease originates unicentrically, usually in a lymph node, and later extends from the lymph node of origin to adjacent lymph nodes via lymphatics. We recently reviewed a series of patients who showed extra nodal extension of Hodgkin's disease in the form of skin invasion and concluded that the skin was invaded by retrograde lymphatic embolization.<sup>2</sup> We have now extended our review to assess the pathogenesis of other sites of extra nodal spread.

#### MATERIAL

The records of 150 patients, including those previously treated, with a histologic diagnosis of Hodgkin's disease were reviewed. These patients were seen from 1936 to 1969. All extra nodal sites of invasion were reviewed and the mode of spread in each patient was scrutinized. The sequence of lymph node extension was recorded and the appearance of each site of extra nodal disease was correlated with the presence or absence of involvement in the regional lymph nodes. Extra nodal disease was also correlated with the presence or absence of systemic Hodgkin's disease. The patient was judged to have systemic Hodgkin's disease when there was more than one site of extra nodal Hodgkin's invasion, or when there were severe systemic signs or symptoms such as anemia, fever and weight loss, or cachexia.

The sites of extra nodal disease were grouped as follows: (1) skin and subcutaneous tissues; (2) epidural tissues; (3) lung; and (4) bone.

Extra nodal invasion of abdominal viscera was not included in this study because ab-

dominal laparotomy and lower extremity lymphography had not been performed on sufficient cases to permit evaluation. However, Kaplan's group<sup>7</sup> has provided much information on this subject.

#### RESULTS

#### SKIN INVOLVEMENT

Twelve of 150 patients showed evidence of skin or subcutaneous tissue invasion of Hodgkin's disease during the course of their illness (Table 1). One patient developed 2 sites of skin involvement during the course of her disease. In 12 of the 13 instances of skin invasion the corresponding regional lymph nodes demonstrated involvement preceding the skin invasion. In the 13th instance, the patient presented with simultaneous involvement of the skin and underlying tissues of the right breast as well as the first echelon lymph nodes consisting of the right axillary, right supraclavicular, and right cervical lymph nodes.

The location of skin affection was random as shown in the composite Figure I, in which each of the 13 sites of skin involvement is shown. The only remarkable and constant feature of these patients was the association of extensive antecedent disease of the lymph nodes draining the territory of subsequent skin invasion. Six of the 13 patients did not show evidence of systemic disease at the time that skin involvement appeared.

In this series there was no instance of direct invasion of the skin from underlying lymph nodes.

Of particular interest is one of the patients, Mr. C.C., age 50 years, who was diagnosed as having clinical Stage II B Hodgkin's disease in 1961. Initial treat-

<sup>\*</sup> Presented at the Fifty-second Annual Meeting of the American Radium Society, Coronado Island, San Diego, California, March 1-4, 1070.

<sup>1-5, 1970.</sup>From the Department of Radiology, Division of Radiation Therapy, State University of New York, Downstate Medical Center, Brooklyn, New York.

TABLE I SKIN INVOLVEMENT

	Pt.	Age	Clinical Stage	Year of Admis- sion	Interval From Onset		volvement al Lymph   Simult.	Systemic Disease Present	Survival After Skin Involvement
I	D.I.	37	IV	1966	0		+	No	4 yr. (A&W)
2	T.C.	61	IIIA	1968	8 mo.	+		No	ı yr.
3	N.E.	53	IV	1960	9 mo.	+		Yes	ı yr.
4	M.A.	36	I	1936	9 yr.	+		Yes	ı yr.
5	B.P.	75	IIA	1963	2 yr.	+		No	2 yr. (LFU)
6	C.C.	50	IIB	1961	2 yr.	+		Yes	3 yr.
7	R.E.	31	IIA	1965	3 mo.	+		No	5 yr. (AēD)
8	P.J.	53	IV	1965	4 mo.	+		No	4 mo.
9	C.B.	24	IIIB	1965	3 yr.	+		Yes	ı yr. (AēD)
IO	F.R.	31	IA	1951	7 yr.	+		Yes	2 yr.
ΙΙ	S.C.	25	V*	1966	2 yr.	+		Yes	ı yr.
I 2	D.V.	18	V*	1959	4 yr.	+		No	3 yr.
13	D.V.	18		1959	5 yr.	+		Yes	Io mo.

\* Stage V-Previous definitive therapy.

A&W = alive and well.

LFU = lost for follow-up.

AcD = alive with disease.

ment was by chemotherapy. Painful axillary lymph nodes appeared in 1962 and local irradiation was given to the right axillary and supraclavicular region by means of orthovoltage equipment; 12×15 cm. parallel opposed fields were utilized and a mid-plane dose of 3,000 r in 3 weeks was delivered. The lower edge of the treatment field reached to just above the nipple.

In 1963 the patient returned with skin invasion located just below the margin of the previously irradiated field. The skin and subcutaneous tissues of the right lateral chest wall and medial aspect of the right arm were affected (Fig. 2).

A right upper extremity lymphogram (Fig. 3) demonstrated complete block in the axilla. Only I lymph node is poorly

opacified, while there are numerous fine collateral vessels passing caudad from the axilla.

In all likelihood the skin was invaded by retrograde lymphatic embolization of Hodgkin's cells.

#### EPIDURAL INVOLVEMENT

Thirteen patients developed epidural extension of Hodgkin's disease confirmed by laminectomy and biopsy in 9 cases and by myelographic demonstration of block in the remaining 4 cases (Table II). Note that the regional lymph nodes in 9 of the 13 patients were clinically involved before the epidural invasion appeared, while in the 4 remaining cases the regional lymph nodes were judged to be involved concomitantly with the epi-

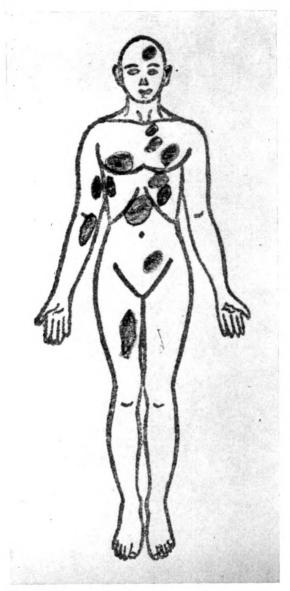


Fig. 1. Composite diagram of 13 sites of skin invasion. Each instance was associated with involvement of the corresponding regional lymph nodes, which preceded the skin disease in 12 of 13 cases.

dural involvement. In 6 of 13 patients systemic disease was not evident at the time of initial epidural invasion.

The site of cord involvement was most closely correlated to the site of predominant lymph node involvement. As a rule patients who showed Hodgkin's disease of the lymph nodes predominantly in the cervical and supraclavicular areas developed epidural

disease in the cervical or upper thoracic region, while patients with mediastinal lymphadenopathy later developed epidural signs at the level of T 11-T 12.

#### LUNG INVOLVEMENT

Ten patients in our series developed pulmonary parenchymal involvement (Table III). Six of the 10 patients showed prior involvement of the regional lymph nodes. In 6 of 10 patients pulmonary lesions appeared before systemic disease was evident. In 7 instances the pulmonary Hodgkin's disease appeared as a single mass or as a lobar consolidation, while the pulmonary manifestations were more diffuse in 3 patients. There was no instance of miliary spread in our series.

#### BONE INVOLVEMENT

Nine patients showed bone involvement (Table IV). In 6 of the 9 patients the regional lymph nodes were diseased prior to the manifestation of bone invasion. Six of the 9 patients showed evidence of systemic disease at the time of bone invasion. The various sites of bone involvement are shown in the composite Figure 4.

#### DISCUSSION

This review has considered the pathogenesis of 45 instances of extra nodal Hodgkin's disease occurring at 4 selected sites:



Fig. 2. Mr. C. C. Skin of right chest and arm is involved by Hodgkin's disease. The right axilla was clinically negative I year after 3,000 r in 3 weeks.

TABLE II
EPIDURAL INVOLVEMENT

	Pt.	Age	Clini- cal Stage	Year of Admis- sion	Location of Lesion	Interval From Onset		volvement aal Lymph   Simult.		Sys- temic Disease Present	Survival After CNS Involvement
Ι	K.J.	74	IV	1965	L <sub>3</sub>	0			+	Yes	15 mo.
2	K.S.	62	V*	1961	Т9-10	3 yr.	+			Yes	I mo.
3	M.F.	64	V*	1962	T1-5	3 yr.	+			No	I mo.
4	B.I.	31	V*	1955	T <sub>9</sub>	0			+	No	4 yr.
5	D.H.	68	IV	1962	Occipital	0	+			No	6 mo.
6	G.B.	57	V*	1967	Т5	2 yr.	+			No	3 yr. (AcD)
7	D.H.	56	V*	1967	T12	2 yr.	+			Yes	2 yr. (AēD)
8	S.T.	58	IV	1969	Т3	1.5 yr.	+			No	6 mo. (AēD)
9	G.J.	49	IV	1967	<b>T</b> 7	0	+			No	2 yr. (AēD)
0	D.V.	18	V*	1959	Tıo	2 yr.	+			Yes	ı yr.
II	S.C.	25	V*	1966	С	7 yr.	+			Yes	ı yr.
2	D.H.	56	IV	1967	Тп	0		+		Yes	2 yr. (AĉD)
3	M.F.	54	IV	1953	T <sub>4</sub> -6	0			+	Yes	10 mo.

<sup>\*</sup> Stage V—Previous definitive therapy.

 $A\bar{c}D = alive$  with disease.

CNS = central nervous system.

the skin, the epidura, the lung, and the bone. In approximately 75 per cent of these 45 instances the corresponding regional or first echelon lymph nodes were demonstrated to be predominantly involved by Hodgkin's disease at a time preceding the appearance of extra nodal tumor.

Direct extension of Hodgkin's disease can be ruled out in the instance of skin involvement because all of the skin lesions were separate from the regional lymph nodes. The same was also largely true for the lung lesions: there was often a clear zone of apparently normal lung between the Hodgkin's infiltrate and the regional lymphadenopathy. In the case of the epidural and bone lesions the evidence was less conclusive. Certainly there was no overt evidence

of direct contiguous extension of lymph node disease. The over-all findings support the hypothesis of retrograde lymphatic embolization as the predominant mechanism of extra nodal spread of Hodgkin's disease in these patients.

Willis<sup>13</sup> pointed out the importance of retrograde lymphatic embolism in 1934 as follows; "... neoplastic replacement of a lymph gland or occlusion of a large lymphatic vessel results in diversion of the lymph flow into devious collateral paths, in some of which there must be reversal of the normal direction of flow. Reversal of flow in lymphatics must take place more readily than in veins, for the circulation of lymph lacks the vis a tergo obtained in the circulation of the blood ... retrograde car-



Fig. 3. Mr. C. C. Lymphogram of right upper extremity. Only one lymph node is imperfectly opacified by a mottled, patchy distribution of contrast medium; numerous fine collateral vessels are faintly demonstrated inferior to the opacified lymph node. The appearance is of lymphatic block with collateralization.

riage of tumor emboli in the lymphatic system is undoubtedly an important factor in the extension of many carcinomas . . . "

Glatstein *et al.*<sup>4</sup> reported on the results of simultaneous liver and aortic lymph node biopsies in 37 previously untreated Hodgkin's disease patients. In 16 patients with positive aortic lymph nodes 8 had a positive liver biopsy. There was no instance of a positive liver biopsy coupled with a negative aortic lymph node biopsy. These data support the hypothesis of extra nodal spread of Hodgkin's disease by retrograde lymphatic extension into the liver.

A pertinent observation is that brain involvement is an extreme rarity in Hodgkin's disease; only 1 of our patients demonstrated brain invasion. The central nervous system is almost unique in not possessing lymphatic vessels. 10 If retrograde embolization is the predominant means of extra nodal spread of Hodgkin's disease, then the rarity of central nervous system invasion seems quite reasonable.

Studies<sup>1,5,7</sup> of patients with untreat Hodgkin's disease have shown a pattern contiguous lymph node involvement, su gesting that the disease extends via ly phatics from a single lymph node of orig to adjacent lymph nodes. The same mo of spread is suggested by a tendency Hodgkin's disease to appear in lymph no groups immediately adjacent to the tre ment fields of previously irradiated region

It has been postulated that the tender of Hodgkin's disease of bone to involve to red marrow is evidence of hematogened metastases. 14 This mechanism is possil correct. On the other hand this review be demonstrated that the site of bone met tases usually is related geographically to to

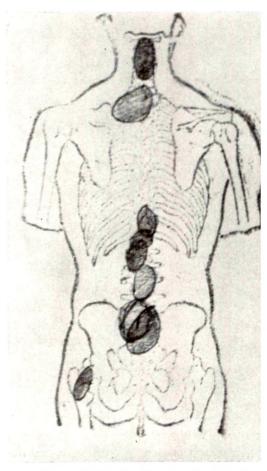


Fig. 4. Composite diagram of 9 sites of bone involvement.

TABLE III

	Pt.	Age	Clinical Stage	Year of Admis- sion	Interval from Onset		volvement al Lymph   Simult.	Systemic Disease Present	Survival After Lung Involvement
I	V.L.	20	IIA	1938	3 mo.	+		 No	ı yr.
2	B.R.	42	v	1941	14 mo.	+		 Yes	3 mo.
3	M.G.	41	v	1964	8 yr.	+		Yes	3 yr.
4	M.S.	28	IVB	1966	I mo.	+		Yes	2 yr.
5	L.I.	35	v	1952	0		+	No	11 yr. (A)
6	T.G.	50	v	1950	0		+	No	ı yr.
7	N.G.	15	IV	1968	0		+	No	2 yr. (AčD)
8	B.Z.	38	IIB	1968	4 yr.	+		Yes	IO mo.
9	O.J.	18	IV	1968	0		+	 No	1 yr. (AčD)
10	A.N.	34	v	1969	6 yr.	+		No	6 mo. (AčD)

A= alive.
AcD= alive with disease.

site of dominant lymph node disease. Possibly the predilection of Hodgkin's disease for red marrow is simply a happenstance, because the regions of frequent lymph node disease, *i.e.*, the central parietal lymph nodes which extend from the neck to the iliac regions, correspond to the red marrow regions of bone.

Lymphography has given insight into the mechanisms of lymphatic spread of tumors and the importance of lymph flow in evaluating the physiology and pathology of the lymphatic apparatus. <sup>6,12</sup> In lymphographic studies of Hodgkin's disease it is not unusual to demonstrate collateralization of lymphatics with functional obstruction of lymph flow in the region of nodes that are invaded. Also, the lymph vessels are described as unusually numerous and thin and often these numerous thin vessels surround the lymph nodes that are affected by the Hodgkin's granuloma. <sup>12</sup>

Experimental lymphography has pro-

vided evidence that obstruction to the normal pathway of lymph causes a prominent retrograde flow of lymph in the lymphatic system.<sup>11</sup>

The data that we have presented provide circumstantial evidence in support of the main hypothesis of this paper, that extra nodal spread of Hodgkin's disease is principally if not exclusively the result of retrograde lymphatic embolization rather than direct invasion by continuity or blood vascular embolization. Nonetheless, these data do not prove the assertion. To prove this assertion it is necessary to carry out physiologic studies in which the neoplastic Hodgkin's cells are tagged in a nondestructive manner such as with tritiated thymidine, following which their path of dissemination is traced to prove that the Hodgkin's neoplastic cells actually do travel via lymphatics and in retrograde flow in the lymphatics as well. Such a proposal envisages extension of current studies

	Pt.	Age	Clinical Stage	Year of Admis- sion	Interval From Onset		volvement al Lymph   Simult.		Systemic Disease Present	Survival After Bone Involvement
I	M.V.	29	I	1933	4 yr.	+			Yes	9 mo.
2	F.B.	45	V*	1941	2 yr.	+			No	4 mo.
3	G.C.	19	V*	1949	8 yr.	+			Yes	4 mo.
4	A.M.	77	IV	1952	0		+		Yes	4 mo.
5	S.L.	59	V*	1955	ı yr.			+	Yes	4 mo.
6	J.S.	17	IV	1954	0			+	Yes	6 mo.
7	J.C.	26	V*	1960	2 yr.	+			No	3 yr. (LFU)

+

+

2 yr.

5 mo.

Table IV
BONE INVOLVEMENT

9

49

J.C.

H.C.

8

done by Engeset and his colleagues<sup>8</sup> who have shown in thoracic duct sampling of patients with Hodgkin's disease that the Reed-Sternberg cell is present in the lymph along with cytologically abnormal reticulum cells. Another study along these lines is that of Peckham and Cooper8 who have used in vitro tritiated thymidine labeling and culture techniques to show that there are a variety of functional as well as morphologic cell types in the lymph nodes of Hodgkin's disease, that some are polyploid, are actively synthesizing DNA, and are probably capable of propagating new colonies of Hodgkin's tumors, while other cells are nonreplicating normal lymphocytes and still others are nonreplicating polyploid Reed-Sternberg cells which seem to be beyond the replicating phase as shown by the absence of tritiated thymidine uptake.

II

III

1961

1962

#### SUMMARY

The pathogenesis of 45 instances of extra nodal Hodgkin's disease occurring at 4

selected sites, the skin, epidura, lung, and bone, was studied in 150 patients. The corresponding regional lymph nodes were involved before the appearance of extra nodal disease in 75 per cent of these patients. In 40 per cent of the cases there was no evidence of other extra nodal disease. Retrograde lymphatic embolization of Hodgkin's tumor cells was postulated as the mechanism of extra nodal spread.

Yes

No

I yr.

3 yr.

The major significance of these findings is that they emphasize the role of lymphatics in the spread of Hodgkin's disease. Extension via lymphatics is probably the predominant mechanism of both internodal and extra nodal spread.

The clinical data also suggest the importance of retrograde flow in lymphatics, a direction of flow that may occur in both inter nodal and extra nodal spread.

Once the concept that extra nodal spread may occur by retrograde lymphatic embolization is accepted, then the implication of extra nodal disease for a given patient is entirely different and each patient must

<sup>\*</sup> Stage V-Previous definitive therapy. LFU=lost for follow-up.

be evaluated individually with a view toward the optimum treatment.

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# A STANDARD SET OF "INDIVIDUALIZED" COMPEN SATING FILTERS FOR MANTLE FIELD RADIO-THERAPY OF HODGKIN'S DISEASE\*

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THE use of wide field techniques in clinical radiotherapy frequently results in considerable tumor dose inhomogeneity because of, in part, the variation in physical characteristics of the irradiated volumes. Such a situation is exemplified by the so-called "mantle field" which is employed in the treatment of Hodgkin's disease (Fig. 1). Although shielding of normal uninvolved tissues such as lung<sup>3.5</sup> has received attention, detailed consideration of the tumor dose inhomogeneities using this technique has only recently been reported. As illustrated by Figure 2, there is a marked difference in the relative depth of the critical

tumor volumes (i.e., lymph nodes) in v ious anatomic sites. The dose distributi is further complicated by the non-norn incidence of the radiations on the patic as produced by the irregular surfaces cluded in the mantle field treatment p tal. In general, the lower mediastinal ar tends to be underdosed using this ter nique as a consequence of: (1) the r atively greater tumor depth than for otl target volumes; and (2) the inheren lower dose rate at the margin of the fie Conversely, the superficial cervical a supraclavicular lymph nodes receive markedly higher daily dose than the m mediastinal lymph nodes.

Both beam modifying and compensatifilters have been used in clinical radioth

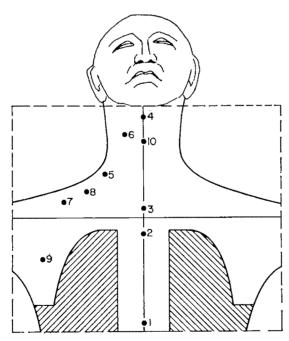


Fig. 1. Diagram of a typical anterior mantle field illustrating the lung blocks and approximate field margins. The numbered points refer to the data in Table II.

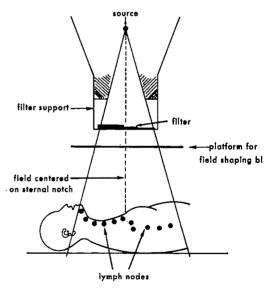


Fig. 2. Diagram of the treatment set-up for mantle field technique showing the relative p tions of the compensating filter, cobalt 60 sou patient, and lymph nodes.

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Fig. 3. Device used to measure the perpendicular source skin distance (SSD) at 20–30 points over the surface of the mantle field portal.

apy for many years.<sup>2,4,6–8</sup> With the advent of megavoltage radiotherapy, compensating filters often replaced bolus so that skin sparing could be preserved. Of particular interest is the design of a filter by Bottrill, Rodgers, and Hope-Stone¹ which compensated for a range of source surface distances (SSD) and modified the dose distribution for treatment of the whole brain and spinal cord.

The present paper describes our technique for "homogenizing" the tumor dose distribution for the mantle field with the application of a standardized set of compensating filters. We have designed a combination filter for use with cobalt 60 tele-

therapy which delivers a homogeneous dose to the various lymph node regions included within the mantle field tissue volume. Initially, these filters were individually constructed for each patient. After analyzing the characteristics of such custom filters for 64 patients, a standard set of components or subfilters was designed from which "individualized" filters could be easily and rapidly assembled. These standard filters have provided as uniform a dose distribution for individual patients as the previously constructed custom filters.

#### **METHODS**

Custom filters were constructed for 64

Table I

LYMPH NODE DEPTHS IN THE "MANTLE FIELD"\*

Depth From Anterior Surface
One-half the anteroposterior diameter
2 cm.
Two-thirds the anteroposterior diameter
3 cm.
One-half the anteroposterior diameter

<sup>\*</sup> The arbitrarily assigned tumor depths are for our technique of irradiating the mantle field through an anterior treatment portal except for the mediastinum which is also irradiated through a posterior portal on alternate days.

patients in the following manner. The perpendicular SSD of 20–30 surface points within the mantle field portal were measured with the device shown in Figure 3. A tumor depth was abitrarily assigned to each point following the scheme shown in Table 1. A relative dose, D, at the tumor depth for each point was calculated from:

$$D = OD \times DD \times (90/SSD)^2$$
,

where OD is the off-axis dose, DD the central axis depth dose for a 30×30 cm. field, and 90 and SSD being the source skin distances respectively to the center of the field and the point being calculated. The off-axis dose (OD) is the ratio of the dose rate at a point off the central axis to the dose rate at the same depth on the central axis (Fig. 4).

Per cent transmission is calculated from the relative dose for each point:

Per Cent Transmission = 
$$100 \times D/D_{\min}$$
,

where D is the relative dose for the point, and  $D_{\min}$  is the minimum relative dose of all points. In nearly every instance,  $D_{\min}$  refers to the relative dose at the lower margin of the mediastinum. The filters were constructed of 1/32 inch copper sheet with the thickness for each portion of the filter being determined from the per cent transmission shown in Figure 5. The copper filter was fastened to a 0.25 inch lucite plate

which fits into the filter holder on the cobalt 60 unit.

The transmission characteristics of these custom filters were checked using LiF dosimetry in a pressdwood phantom. Each point used to determine the filter was checked with dosimeters being placed at the appropriate coordinates (depth, SSD, and distance from the central axis). Dosimetric measurements were made for the following number of points under each filter: 5-9 in the mediastinum, 5-8 in the midline neck, 3 in each axilla and each side of the neck, and 2 in each supraclavicular region. On the average, the tumor dose at the various points under the filters was 4,000 ± 165 rads with an intended uniform tumor dose of 4,000 rads.

The information collected in designing

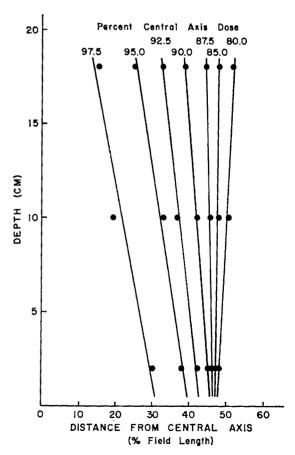


Fig. 4. Decrement lines for field sizes greater than 20 cm. square for the Theratron 80 cobalt 60 unit.

these 64 custom filters was then reviewed and 4 anatomic areas were identified for purposes of determining the measurement ranges. For each of the 4 anatomic areas, namely the midline cervical-supraclavicular, lateral neck, axillary, and mediastinal areas, a set of subfilters was constructed to encompass the range of measurements encountered in the 64 custom filters. These subfilters have been constructed of brass which has nearly the same absorption coefficient as copper (Fig. 5) but better machining properties. The subfilters are combined in an appropriate manner for each patient to form a composite filter as schematically illustrated in Figure 6. In this fashion, a semi-customized compensating filter can be assembled rapidly for each individual patient with a standard set of components. It has been demonstrated with LiF dosimetry that these standard filters produce as homogeneous a dose distribution as the more laboriously constructed custom filters. Table II summarizes a representative dose distribution measured in a Machlett-Alderson Rando Phantom Man with thermoluminescent dosimeters. The points selected for measurements are those schematically illustrated in Figure I using the tumor depths given in Table I.

The requirement for using these standard compensating filters for mantle field radiotherapy is adherence to a consistent treatment plan. The center of the field (central axis) must be precisely reproducible for each patient so that the break in filter thickness between the lower midcervical and mediastinal subfilters will remain centered over the sternal notch. Likewise, our filters have been designed for placement in a filter holder located 45 cm. from the source. For other relative filter locations between the source and patients as well as for other treatment distances, the subfilters need only have their size adjusted, this scaling easily being done using the similar triangles concept from plane geometry.

#### DISCUSSION

Even after long experience, the construc-

tion of individual custom filters from the mantle field technique continued to require a considerable amount of time. The entire procedure took several hours including measurement of the patient contour, calculation of thickness and design of the filter. reduction in size for beam divergence, and final construction. Utilizing the standard set of subfilters, "individualized" compensating filters can be assembled in about 15 minutes including the time for patient measurement. The only measurements required to select the correct subfilters for a specific patient are 4 anteroposterior patient thicknesses and 2 source surface distances at preselected points in the field. And it has been our experience that the required standardization of the treatment, such as centering the field at a uniform location, is not a constraint to the radiotherapist. Rather, standardization has tended to facilitate the daily reproduction of accurate treatment conditions for the medical and technical staff alike.

A variety of treatment port arrangements may be used for irradiation of the mantle field. A single anterior field tends to overdose the anterior mediastinal structures including the heart, although the cervical, supraclavicular, and axillary regions can be satisfactorily irradiated through an anterior field only, particularly when the arms are extended over the head to expose the axillae. A second option is the use of parallel opposing mantle fields which requires the alternating of the patient between the supine and prone positions during successive treatments. This can be accomplished but requires considerable care to obtain perfect matching of the anterior and posterior fields. It has been our experience that it is relatively simpler to treat the entire mantle field through an anterior field except for the mediastinum which on alternate days is irradiated through a posterior port. This permits the patient to remain in the supine position and takes advantage of the isocentric mount of the Theratron 80 for precise matching of the anterior and posterior mediastinal ports.

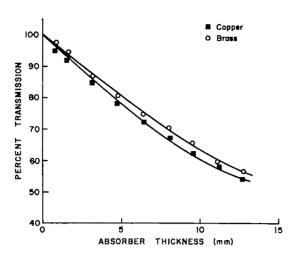


Fig. 5. Transmission of cobalt 60 gamma rays by copper and brass.

Unless compensating filters are employed, a "shrinking field" technique is usually followed, whereby the field size is appropriately reduced as the desired tumor dose to different lymph node areas is reached. With this technique, the time-dose relationship to different areas varies considerably. With the compensating filters, all lymph node areas receive the desired tumor dose at the same dose rate. This has resulted in visibly more uniform skin reactions and has improved patient tolerance to treatment, especially by reducing the radiation pharyngitis caused by intensive dose fractions to the cervical region. Introduction of these compensating filters into routine use has not compromised the therapeutic effectiveness in any manner. During the past 30 months, during which time

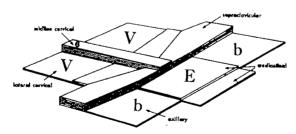


Fig. 6. Diagram of an assembled standard filter. The numbers and letters identify the subfilters which form the composite filter.

TABLE II

DOSES TO POINTS IN THE MANTLE FIELD IRRADIA:
WITH COBALT 60 TELETHERAPY USING A
STANDARD FILTER TECHNIQUE

Area	Point*	Measured Tur Dose (rads)
Lower Mediastinum	I	4,160
Upper Mediastinum	2	4,100
Lower Neck (midline)	3	4,260
Upper Neck (midline)	4	4,180
Lower Neck (lateral)	5	3,740
Upper Neck (lateral)	6	4,120
Supraclavicular	7	4,060
Supraclavicular	8	4,340
Axilla	9	3,780
Spinal Cord		
(T 10)		4,100
(T <sub>4</sub> )		4,420
(C 3)		3,140

<sup>\*</sup> The numbers refer to the points shown schematicall Figure 1.

80 patients with Hodgkin's disease habeen treated with the use of compensat filters, only one recurrence has develop within the treated field. This recurrence was observed at the margin of the treater area and was quite likely the result of und dosage due to suboptimal field placeme

#### SUMMARY

On the basis of experience with constr tion of custom compensating filters for patients treated with mantle field te niques for Hodgkin's disease, a stand set of component parts has been design "Individualized" compensating filters now be rapidly assembled which corr for both the range in source surface ( tance to different areas and the variat in depth of the lymph nodes in seve different anatomic regions. These filt have been constructed for positioning the filter holder under specified treatm conditions, using cobalt 60 telethera Modification is relatively simple for use the filters at different source filter : source patient distances by appropri scaling of size. Both phantom measu

ments and clinical experience have demonstrated the resulting improvement of dose homogeneity.

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Patent is pending on the specifications for construction of this filter device. Individuals interested in the details of construction and methods of modification for various treatment conditions may write the senior author.

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# VARIABLE BLOCK-SURFACE-DISTANCE (BSD) FOR ADJUSTMENT OF SHADOW SIZE IN MANTLE THERAPY\*

By YOSH MARUYAMA, M.D.,† and FAIZ M. KHAN, Ph.D. With the assistance of Dennis Burns MINNEAPOLIS, MINNESOTA

FIELD shaping for megavoltage beams is complex. For example, radiation therapy of large irregular fields is currently being employed for special radiotherapeutic situations with considerably increased frequency. The entire supradiaphragmatic lymph node bearing structures may be treated in Hodgkin's disease in a field commonly referred to as the "mantle" field.2.5 The lungs are excluded from the radiation field by lead blocks, which may either be a series of standard blocks for all patients1 of similar size and shape, or individualized for each patient.4 Certain problems arise in the use of irregularly shaped radiation therapy fields. For example, penumbra and boundary dose distribution of shielded volumes vary with block position, as well as the central axis dose rate in the irradiated field.3

The shadow of blocks designed to shield a volume may sometimes show discrepancies from desired shadows on the port film. The use of variable block-surface-distance (BSD) permits small adjustments of block shadow to be made to conform as closely as possible to the volume to be shielded. Maximum differential dosage between normal and tumorous tissue is thereby possible.

# SHIELD POSITION AND SHADOW SIZE

Consider the radiation as emanating from a point (P) source (Fig. 1). A shield s, represented by a line, is interposed in the radiation field. If it absorbs all incident radiation, then it casts a shadow S where primary dose is absent. The ratio s/S of shield to shadow size is equal to x/b (x=

source to block distance; b =source to surface distance).

Now if the shield is moved a small distance  $\Delta x$ , then the new shadow size S' is related to the old shadow size by

$$S' = S + \Delta S. \tag{1}$$

Consider the adjustment problem for a given shield to obtain a shadow of required size. This follows:

$$\Delta S = \frac{bs\Delta x}{x(x + \Delta x)},\tag{2}$$

that is, the change in shadow size  $\Delta S$ , relative to original size S, is produced by a change in block position  $\Delta x$  which can be determined from distances x, b and shield size s.

## SHADOWING FOR BLOCKS OF FINITE THICKNESS

The geometric considerations for a block s of height a placed a distance l from the central axis is shown in Figure 2. When the block is placed with its medial surface along the central ray (l=0), then the shadow is determined by the upper surface; no partial transmission zone is present on the medial shield border; the partial transmission zone is determined by block height a and applies only to the lateral border. Consider a block positioned with its medial border on the central ray (l=0); the partial transmission zone  $\delta$  follows:

$$\frac{\delta}{S} = \frac{a}{x+a}. (3)$$

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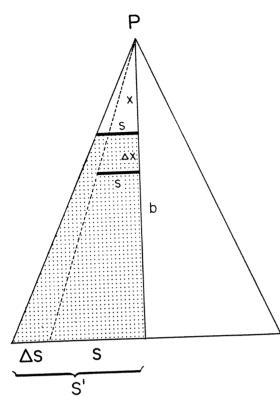


Fig. 1. A point (P) source of radiation emits rays which are absorbed by shield s, represented by a line, casting a shadow s on the surface. A movement of the shield by s alters the shadow by s.

Figure 3 tabulates this relationship as a percentage value, for small blocks at a variety of positions x/b, and for block sizes of 5 cm., 7.5 cm. and 10 cm. Inspection of the data shows that the least dose gradation zone is observed when a small (5 cm.) block is placed close to the surface and next to the central axis. When the block is placed close to the source, this zone becomes large enough to become a serious consideration.

When the medial surface is placed a distance *l* from the central axis (Fig. 2), then the block face contributing to the shadow varies with parameters

$$\frac{l}{l+s}$$
, block position x, and block height a.

Likewise, there is a medial and lateral partial transmission zone, here noted as

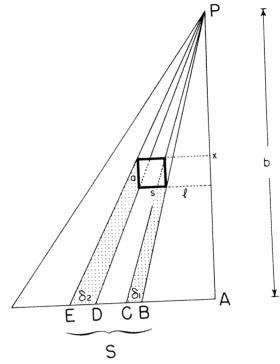


Fig. 2. Geometric considerations for a block shield in a radiant field emitted by a point (P) source of radiation. The distance *l* should be considered radial distance from the central axis ray.

 $\delta_1$  and  $\delta_2$  of which the lateral border is the major contributor. These zones contribute to increase the transmission inhomogeneity of the shielded zones. Beam divergence correction eliminates this inhomogeneity in the primary beam.

From geometric considerations of Figure 2, it can be shown that the medial partial transmission zone  $\delta_1$ , and the lateral zone  $\delta_2$  follow:

$$\delta_1 = bl \left[ \frac{1}{x} - \frac{1}{x+a} \right], \text{ and }$$
 (4)

$$\delta_2 = b(l+s) \left[ \frac{1}{x} - \frac{1}{x+a} \right]. \tag{5}$$

Since EB is the shadow zone, the shielded zone follows

$$S = b \left[ \frac{l+s}{x} - \frac{l}{x+a} \right], \tag{6}$$

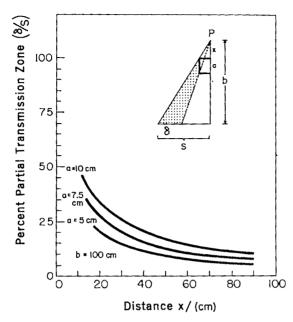


Fig. 3. Relationship of partial transmission zone to relative distance x for a block shield of various heights.

which is simply the sum of the various components of the block shadow.

To produce a change in the shadow size,  $\Delta S$ , by small adjustments of distance  $\Delta x$ , the relationship follows:

$$\Delta S = b \left[ \frac{l+s}{x+\Delta x} - \frac{l+s}{x} + \frac{l}{x+a} - \frac{l}{x+\Delta x+a} \right]. \tag{7}$$

From this relationship, any required change in shadow size can be made by an appropriate change in block position. Adjustments can readily be made either in relation to the source or the surface (BSD). In general, shadow changes are most sensitive to block movement when a large block is positioned close to the source, and away from the central axis. This is shown in Figure 4.

An example illustrates the problem.

Example: A patient with thoracic diameter of 20 cm. is positioned at a source-skin-distance of 80 cm. The source to table distance is 100 cm. A lead shield,

5 cm. wide and 5 cm. high is placed in the field and produces an image on the port radiograph (placed at the table) which is 2 cm. too wide. The block is positioned at a distance of 40 cm. from the source and 5 cm. lateral to the central ray. Where should it be positioned to produce the required shadow?

Answer: The shield should be moved to a new source-block-distance of 46 cm.

# EFFECT OF FIXING THE INTERBLOCK DISTANCE

It has been suggested that a convenient technique for accurate separation of mantle shields conforming to mediastinal dimensions is to fix the interblock distance at the appropriate distance using plastic foams.<sup>4</sup> Since the diameter of the thorax usually differs by no more than 1–3 cm. in the anteroposterior and posteroanterior positions, one may consider the effect of small changes in BSD on interblock distance. The unshielded portion (a) will become smaller as the BSD is decreased, and larger as the BSD is increased, as described above for a shield.

#### DISCUSSION

Certain problems of field shaping for megavoltage radiotherapy have been considered based upon geometric adjustments of block position relative to source and to the object to be "shadowed" or protected from the radiant beam. Precise adjustments for shadowing problems encountered in megavoltage x- or γ-ray therapy can be easily made. One problem of contemporary interest concerns adjustments of radiation field size for mantle therapy. Rather than recutting or recasting lung shields, considerable adjustments can be made by a table with vertical motion which can vary the block-surface-distance. Such a table is shown in Figure 5 and the adjustment problem illustrated in Figure 6 for a mantle field.

Source penumbra considerations and scattered dose effects for block position

## Lateral Displacement and Shield-Shadow Size Change

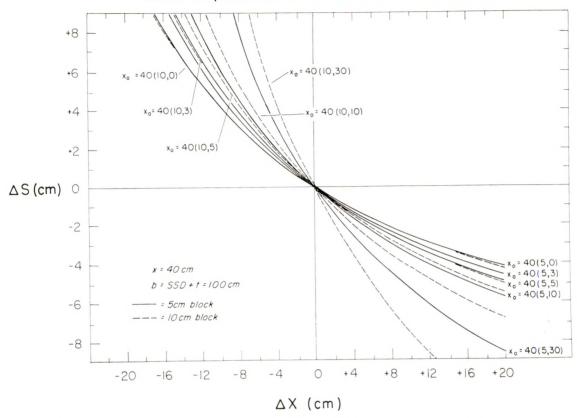


Fig. 4. Relationship of displacement from the central axis and block movement upon change in shadow size. Solid line for 5 cm. height blocks; dashed lines for 10 cm. height blocks. Initial block position  $x_0$  noted by  $x_1$ , (a, l) on the figure.

have not been considered in this paper. They further increase shadow unsharpness and dose gradation zones in each situation. For radiation sources of finite size, it is clear that source penumbra is also affected by block position, is minimized by shorter BSDs and increases partial transmission zones.

In shielding problems, the considerations pointed out in this paper indicate some of the problems encountered. We have found that thoracic size is not always the same on the anteroposterior and posteroanterior port. If the same reversible shield is to be used for a protection problem, we have favored the use of the smaller diameter chest radiograph as the template for shield construction. We have then adjusted the block-surface-distance to the required

distance for the larger diameter chest. Minor corrections are readily made using this approach. Adjustments for differences in thoracic configuration between the anteroposterior and posteroanterior patient ports can thus be easily made by the variable block-to-surface distance (BSD) method. The computational adjustment using Equation 7 is precise and a single port radiograph need be taken, the adjustment determined, and table adjustment carried out by a vertical height adjustment for a shield of known dimensions. In practical use, the appropriately marked port film can be placed at the source-table distance. The shield can then be moved in the light field until the shadow conforms to the required configuration of the shadow area, and the BSD recorded. The patient is

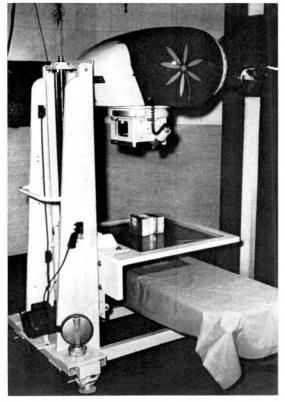


Fig. 5. Table with vertical motion to adjust the position of blocks in vertical direction.

then treated at the noted BSD which the proper block-to-surface distance. 'latter may be designated the "confortional" method.

#### CONCLUSION

The problem of shield-shadow adjuments have been considered in this par Several factors contribute to shadow s penumbra and partial transmission of I blocks. These relate to: (1) source size; block height; (3) beam divergence; position lateral to central axis; (5) blo surface-distance; and source-surfacetance (SSD). A number of these fac can be manipulated to minimize the pr lems discussed for any given unit or tre ment situation. Variable BSD is one met of optimal and individualized radiothera tailoring treatment fields to the the peutic problem. The adjustment can done by either a computational or "c formational" method. The use of a 1 tin sheet on the surface of the table duces secondary electron contamination the beam<sup>3</sup> and permits block usage ur

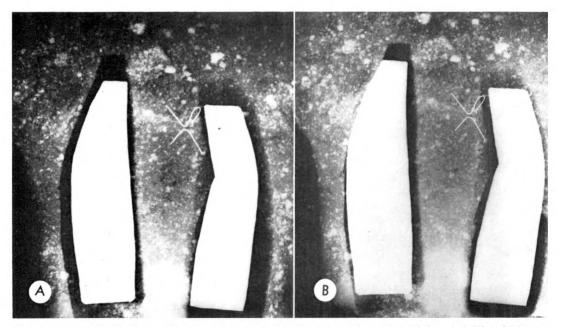


Fig. 6. (A and B) Radiographs of manikin with shield over simulated lung fields. (A) The shield wa small at BSD, but (B) was adjusted to correct the BSD to proper position. Computational method mitted accurate adjustment.

more favorable conditions, positioned close to the patient.

#### SUMMARY

The problem of blocking an irradiation field has been considered based upon geometric principles. Precise adjustments of field shadowing can be made according to the method described.

Considerable adjustment of shielded areas can be obtained by a block table which can be varied in its vertical position. A practical method is described.

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We wish to acknowledge that the moving

table top shield tray was constructed in the Scientific Apparatus Shop under the direction of Mr. Lawrence Espy.

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# ADVANCED, RECURRENT AND/OR UNUSUAL METASTASES IN CHILDHOOD MALIGNANCIES\*

# ILLUSTRATIONS OF A "PHILOSOPHICAL" APPROACH TO THE USE OF RADIATION THERAPY

By MELVIN TEFFT, M.D. BOSTON, MASSACHUSETTS

In 1966, Farber<sup>2</sup> reported the results of the treatment of children with Wilms' tumor who had been admitted to the Children's Hospital Medical Center between 1957 and 1964. In that report, he noted a striking increase in survival of patients since the use of actinomycin D, as compared to those patients treated without actinomycin D, before 1957. Moreover, there was a marked difference in survival in favor of those children who were treated from the time of original diagnosis at this Center, as compared to those referred at some time thereafter.

The present report is to emphasize, from that experience, that a combined oncologic approach to management, which includes radiation therapy, may result in long-term control despite far advanced and/or recurrent metastases. For purposes of illustration, we have selected the problem of Wilms' tumor, metastatic to the lungs. In addition, we have selected certain patients with other types of neoplasm to illustrate that this persistent therapeutic approach may result also in a similar favorable outcome.

#### MATERIAL

The patients chosen to illustrate the effectiveness of a rational persistent approach to therapy were selected because of their special interest from a total of 356 patients with Wilms' tumor, 350 patients with neuroblastoma, 139 patients with undifferentiated rhabdomyosarcoma, 115 with osteogenic sarcoma, and 93 with Ewing's sarcoma who have been treated in the De-

partment of Radiation Therapy, Childre Hospital Medical Center, since 1940. Specifically, this includes the children, w Wilms' tumor, first diagnosed and treat at this Center, and those referred here some time following initial treatment another institution.

#### REPORT OF CASES

CASE I. Patient R.M. This boy was 2 years of age when he developed gross hematur and was found to have a right abdominal mas He was admitted to another hospital where diagnosis of a right Wilms' tumor was mad Lung metastases were present at diagnos (Fig. 1A). At laparotomy, total removal of tl tumor and affected kidney was accomplishe Postoperatively, he received 3,000 rads in days to the right renal fossa and 1,280 rads 10 days to both lung fields. Actinomycin I 60 γ/kg. body weight, was administered cor comitantly. Following therapy, his pulmonar metastases regressed completely (Fig. 1B) an he remained well for the next 5 months. Durin this latter period, one additional course c actinomycin D was administered, at simila dose. At the end of this period, he developed mass in the right testicle and spermatic cord recurrent bilateral pulmonary metastases wer noted at this time also (Fig. 1C). He was re ferred to the Children's Hospital Medica Center where he underwent a right radica orchiectomy. The diagnosis of metastatic Wilms tumor was confirmed. Postoperatively, he re ceived 2,050 rads in 11 days to the right lowe abdomen to include the ipsilateral iliac lympl nodes, and 1,210 rads in 8 days to both lung fields. A course of actinomycin D,\* at 60  $\gamma/\mathrm{kg}$ 

\*At this Center, all chemotherapy is administered under the direction of Dr. Sidney Farber.

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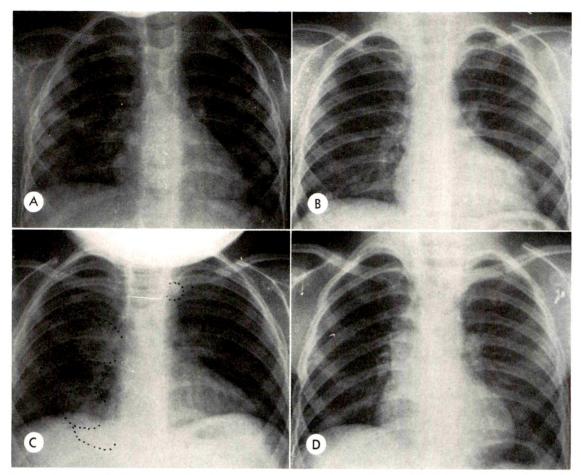


Fig. 1. Case 1. (A) Posteroanterior chest roentgenogram at diagnosis of Wilms' tumor. There are severa metastatic foci throughout both lung fields. (B) Following treatment with 1,280 rads to both lung fields and actinomycin D, the lesions have regressed. (C) Four months later, recurrence of metastatic lesions to both lungs is noted. At this time, he had metastases to the right testicle and spermatic cord. (D) A repeat course of irradiation (1,210 rads to both lungs) plus actinomycin D resulted in regression of this second recurrence of lung metastases. He remains well at 11 years following diagnosis.

body weight, was administered at this time. His lung lesions regressed completely (Fig. 1D) and he remains free of recurrence to the present time, or 11 years later.

Case II. Patient K.S. This boy was  $2\frac{1}{12}$  years of age when his parent noticed an asymptomatic mass within the left abdomen. Upon admission and evaluation at another hospital, a diagnosis of Wilms' tumor of the left kidney was made. At laparotomy, total resection of the tumor and affected kidney was accomplished. No metastases were noted at this time, although the left renal vein contained a tumor extension—no involvement of the inferior vena cava was observed. Postoperatively, he received

2,400 rads in 38 days to the left renal fossa, but no concomitant chemotherapy. He remained well for the following 7 months when he developed widespread pulmonary metastases (Fig. 2A). No metastases at other sites were observed. He was admitted to this Center, where a thoracentesis confirmed the presence of malignant cells in the pleural fluid, compatible with Wilms' tumor. A dose of 1,210 rads in 11 days was delivered to both lungs in conjunction with actinomycin D at 85  $\gamma$ /kg. body weight. Over the next 2 months, his pulmonary metastases regressed (Fig. 2B). However, at the end of this period, recurrence was noted at one site (Fig. 2C). Additional irradiation was delivered to the local site—i.e., 1,860 rads in 31 days was

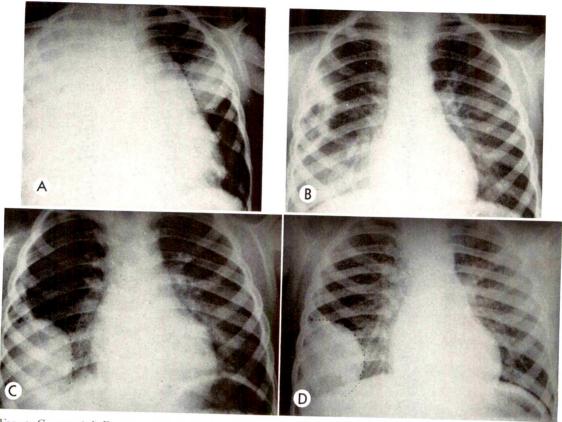


FIG. 2. Case II. (A) Posteroanterior chest roentgenogram shows opacity of the right hemithorax due to fluid and probable parenchymal metastases. Metastatic foci are present in the left hemithorax. The heart and mediastinum are shifted to the left. (B) Two weeks following therapy, further resolution of metastatic disease is evident. A residual focus remains along the right pleural surface. (C) Ten weeks following treatment, there is recurrence in the right lower lung field, and probable associated pleural effusion. (D) Three months following additional higher local dose irradiation to the right lower lung field (plus actinomycin D), the lesion at the right base is unchanged; no other lesions have recurred, however. He remains well for the past II years following thoracotomy to the right lung.

delivered to the right lower lung field; 80  $\gamma/kg$ . body weight actinomycin D was administered concomitantly. Over the ensuing 3 months, no regression of this local lesion was observed; however, no further recurrence became apparent (Fig. 2D). At this point in time, he underwent a thoracotomy and right lower lobe lobectomy, which included removal of pleura and a portion of the right hemidiaphragm. Pathologic examination confirmed metastatic Wilms' tumor and revealed "radiation reaction." Since that time, he has received 7 additional courses of actinomycin D over a period of 21 months following thoracotomy and he remains free of further recurrence for the past II years.

Case III. Patient C.T. This  $4\frac{8}{12}$  year old boy was admitted to the Children's Hospital

Medical Center with a left-sided abdominal mass. Diagnostic evaluation led to a diagnosis of left Wilms' tumor; no metastases were present. At laparotomy, the neoplasm was resected completely; perirenal lymphatic invasion was found at pathologic examination. Postoperatively, he received 2,950 rads in 26 days to the left renal fossa and concomitant actimoycin D at 70  $\gamma/\mathrm{kg}$ . body weight. He remained free of active disease over the ensuing 6 months, when he then developed metastases to the mediastinum (Fig.  $3\vec{A}$ ). No metastases were observed in the peripheral lung fields. A dose of 1,200 rads was delivered in 10 days to both lung fields in combination with actinomycin D (at 70  $\gamma/kg$ . body weight) and the lesion regressed completely. He continued to do well, without further therapy, over the next 15 months, but then developed a solitary meta-

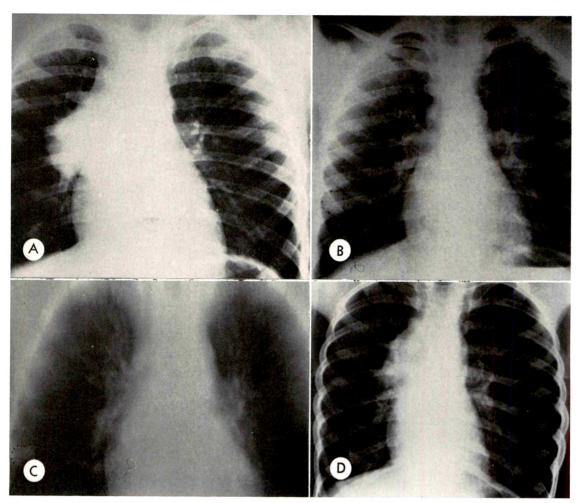


Fig. 3. Case III. (A) Posteroanterior chest roentgenogram, taken 6 months following excision of a left Wilms tumor, shows a mediastinal mass. No metastases are noted in the peripheral lung fields. (B) Posteroanterior roentgenogram of the chest, taken 15 months later, reveals a solitary metastatic focus in the right lung. Following irradiation and actinomycin D this completely disappeared. (C) Four months later, however, the lesion in the right mid-lung field has recurred, as noted on this laminagram. No other lesions in the lungs were evident. A wedge resection of this lesion was performed. (D) Ten months following thoracotomy, he has developed a recurrence of the mediastinal mass noted in A.

static focus in the right mid-lung field (Fig. 3B). A dose of 1,340 rads in 9 days was directed to both lung fields in conjunction with actinomycin D (at a dose similar to that administered previously). At the completion of this treatment, the lesion regressed completely but recurred 4 months later (Fig. 3C). At this time, chest laminagrams revealed no other lesions; he underwent a right thoracotomy and wedge resection of this single focus. Pathologic examination confirmed metastatic Wilms' tumor and revealed involvement of adjacent lymphatic vessels. He continued to be free of active disease and was well over the ensuing 10 months,

at the end of which time he developed a recurrence of his initial metastatic focus—i.e., the mediastinum. This was believed to represent involvement of mediastinal lymph nodes (Fig. 3, D and E). At this time, he received an additional 3,000 rads in 19 days to the mediastinum and hilar lymph nodes, in conjunction with actinomycin D (70  $\gamma$ /kg. body weight). This lesion regressed completely (Fig. 3F). He remains free of further recurrence to this time, or 5 years following treatment for his last evidence of metastasis. Follow-up chest roent-genogram reveals changes in the mediastinum due to irradiation (Fig. 3G); thus far, he re-

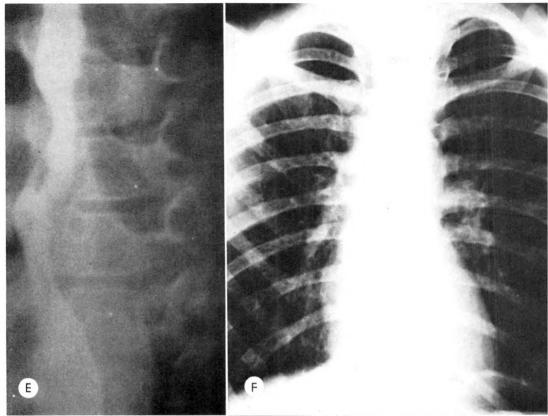
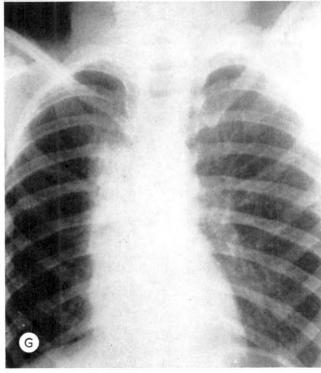


Fig. 3. (E) The mediastinal mass indents the barium-filled esophagus; it is probably due to enlarged mediastinal lymph nodes. (F) At the conclusion of 3,000 rads to the mediastinal and hilar lymph nodes (plus actinomycin D), the chest roentgenogram has returned to normal. (G) A chest roentgenogram 7 months later shows mediastinal fibrosis. More recent chest roentgenograms show similar nonprogressive changes. No further metastases have occurred in the past 5 years.



mains asymptomatic despite the evident fibrosis.

Case IV. Patient D.R. This  $2\frac{9}{12}$  year old girl was found to have a left abdominal mass I week following the onset of gross hematuria and abdominal pain. She was admitted to the Children's Hospital Medical Center where, in addition to the abdominal mass and hematuria, her blood pressure was found to be 190/130 mm. Hg. Following diagnostic evaluation, a left Wilms' tumor was excised completely; the left renal artery was found to be compressed externally by tumor-her blood pressure returned to normal levels, postoperatively. She received 2,910 rads in 25 days to the left renal fossa, plus 60  $\gamma$ /kg. body weight actinomycin D in the postoperative period. Six weeks following the completion of this course of treatment, she received a second similar course of actinomycin D. She remained well over the ensuing 14 months when she then developed a metastatic focus in the right lower lung field (Fig. 4A). A dose of 1,310 rads in 9 days was delivered to both lung fields, in combination with actinomycin D, at 70  $\gamma/\text{kg}$ . body weight, and the lesion regressed (Fig. 4B). She remained well for another 12 months when the same metastatic focus recurred (Fig. 4C); no other lesions were evident by chest laminagrams. A dose of 1,320 rads in 9 days was delivered to both lung fields, again in combination with actinomycin D at similar dosage to that previously described. Once again, the lesion regressed completely and she remained free of active disease for 12 months more, when a lesion recurred at the same location (Fig. 4D). No other metastatic foci were evident on chest laminagrams, and she underwent thoracotomy and wedge resection of this lesion. Because tumor was found at the margin of resection, she received 1,900 rads in 15 days to the right lower lung field; on this occasion, irradiation was combined with vincristine sulfate (0.05 mg./kg. body weight per dose) which was administered once per week for 4 consecutive weeks. Since that time, she has remained free of recurrence, at 6 years from this last metastasis.

Case v. Patient D.D. This  $5\frac{6}{12}$  year old boy was admitted to another hospital with a left abdominal mass. Following evaluation, he underwent a laparotomy and a left Wilms' tumor with the affected kidney was excised completely.

Postoperatively, he received 3,300 rads in 29 days to the left renal fossa, but no chemotherapy was administered. Six months later, he developed a large mass involving the left upper lung field, with possible involvement of mediastinal structures also. He was admitted to this Center and treated with 1,260 rads to both lung fields, plus actinomycin D (60  $\gamma$ /kg. body weight). Complete regression was observed (Fig. 5, A and B). Five additional courses of actinomycin D were administered over the following 8 months. He remains free of recurrence to the present time, or 9 years following original diagnosis and treatment.

Case vi. Patient S.H. This girl was  $2\frac{1}{12}$ years of age when, in 1956, she developed a mass involving the right upper eyelid. Following admission to another institution, biopsy revealed undifferentiated rhabdomyosarcoma and she underwent a radical orbital exenteration. Tumor was present at the cut end of the optic nerve. She was then referred to the Children's Hospital Medical Center, where she received 3,100 rads in 38 days to the retro-orbital region, in conjunction with an antifolic chemotherapeutic compound. One month following completion of this course of irradiation, she developed an enlarged right submandibular lymph node which, at biopsy, proved to be metastatic rhabdomyosarcoma. A radical right cervical lymph node dissection was performed; no further lymph node metastases were present at pathologic examination. Thereafter, she received 3,070 rads in 44 days to the site of radical neck dissection, plus concomitant actinomycin D at doses similar to those described for the previous patients. Three months following this course of therapy, she developed a recurrence overlying the ramus of the right mandible—just within the margin of previous resection, but outside the portal of previous irradiation. The mass was adherent to periosteum of the right hemimandible and attached to the fascia of the masseter muscle; therefore, surgical excision was incomplete. Following this partial excision, she received 3,130 rads in 18 days to the local site, and another course of actinomycin D. Since that time, she has remained free of further recurrence for the past 13 years.

Case VII. Patient R.S. In 1956, this  $7\frac{3}{12}$  year old boy developed a soft tissue mass about,

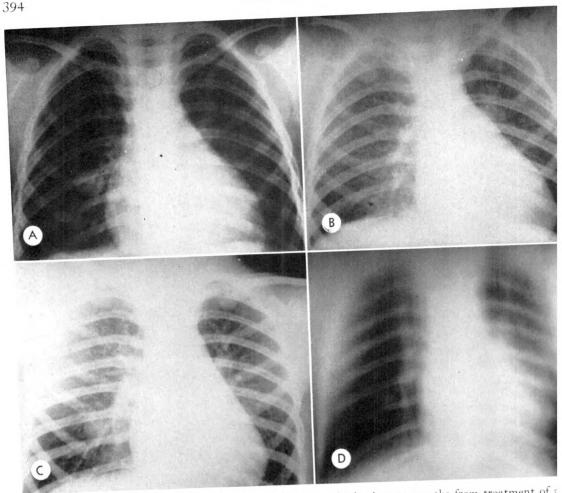


Fig. 4. Case IV. (A) Posteroanterior chest roentgenogram, obtained at 14 months from treatment of a Wilms' tumor, shows a single metastatic focus in the right lower lung field. (B) Following completion, 310 rads to both lungs and actinomycin D, the focus has regressed. (C) Posteroanterior roentgenog of the chest, I year later, shows a recurrence of this lesion; no other lesions are evident. Following addit 1,320 rads to both lung fields (and actinomycin D), this focus regressed completely. (D) Twelve more later, or 24 months following its first appearance, the lesion has recurred in the right lower lung fields shown by this laminagram. Once again, no other lesions are evident. At this time, she underwent a versection. She remains well at 5 years.

and destruction of, the shaft of the left fibula. Biopsy revealed Ewing's sarcoma (Fig. 6A). He received 6,070 rads in 49 days to the entire shaft of the left fibula plus chlorambucil. Follow-up roentgenograms revealed regression of the soft tissue mass (as was apparent clinically) and "healing" of the fibular lesion, which remains under control to this time (Fig. 6B). However, 7 months following completion of this course of irradiation, he developed a solitary metastatic focus at the left costophrenic sulcus (Fig. 6C). A dose of 3,000 rads in 36 days was delivered to this local site, in conjunction with actinomycin D (77  $\gamma$ /kg. body weight). Com-

plete resolution of this lesion was achi (Fig. 6D) and no recurrent lung metastases been observed since that time. Over the en 27 months, he received 2 additional cours actinomycin D as prophylaxis (100  $\gamma$  60  $\gamma$ /kg. body weight, respectively) an mained well until the end of this peritime. In November, 1959, however, he coped ptosis of the right upper eyelid, prophthalmoplegia, and proptosis of the eye. Roentgenograms revealed osteolyt struction of the superior rim of the right orbit (Fig. 6E). A dose of 6,000 rads in 5 was delivered to the right orbit and re-

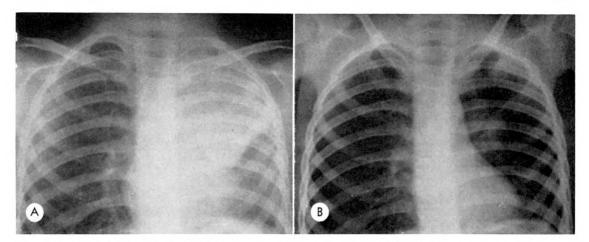


Fig. 5. Case v. (A) Posteroanterior chest roentgenogram, taken 6 months following resection and treatment for Wilms' tumor, shows a large density in the left upper lung field. (B) Following 1,260 rads to both lung fields, and actinomycin D, the lesion has regressed. He remains well at 9 years.

bital areas by rotation, with a 2 cm. lead "hammer" used to shield the lens; concomitant actinomycin D was administered (60  $\gamma/kg$ . body weight). Since that time, he was maintained on oral cytoxan (50 mg./day) for a period of 4 years. As of this date, or 11 years since his last evidence of metastasis, he is free of recurrent disease. His eyesight is unimpaired (Fig. 6F).

Case VIII. Patient C.L. At age 16 years, this boy was found to have a destructive lesion of the left distal femur. Biopsy at another institution revealed osteogenic sarcoma and he underwent amputation. He remained well for 2 years, when he developed a single metastatic focus in the right lower lung field on a routine chest roentgenogram. He underwent thoracotomy and right lower lobectomy at this time. He remained free of obvious metastases for the next 6 months, when he then developed 2 foci: 1 in the upper lung field, and 1 at the hilum of the left lung (Fig. 7A). He was referred to this Center where he was treated with 1,030 rads

in 17 days to both lung fields and mitomycin C (5 doses, 100  $\gamma$ /kg. body weight per dose). Following this treatment, the 2 metastatic foci



Fig. 6. Case VII. (A) Anteroposterior view of the left fibula, prior to treatment, reveals a diffuse "mottling" of trabecular architecture due to bone infiltration by Ewing's sarcoma. A soft tissue mass is evident. (B) Anteroposterior view of the fibula, 4 years following irradiation (6,070 rads), shows the bony architecture to have returned to normal. It remains so to this date, or 14 years from diagnosis.

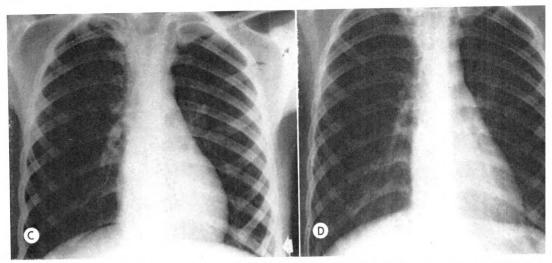


Fig. 6. (C) Posteroanterior roentgenogram of the chest, taken 6 months following treatment for his princlesion, reveals a single density at the left costophrenic sulcus (arrow). (D) Four months following delicity of 3,000 rads to the left costophrenic angle (and actinomycin D), this process has regressed. His roentgenograms have remained clear to this date.

regressed within the ensuing 2 months; after I more month had elapsed, however (3 months from the completion of lung irradiation), the left upper lobe focus recurred (Fig. 7B). Over the next 4 months, it remained stationary and began to calcify; during this time interval, the left hilar lesion recurred. Seven months following his lung irradiation and mitomycin C therapy, he underwent a left thoracotomy: the 2 lesions were removed by wedge resection. The diagnosis of metastatic osteosarcoma was confirmed at these sites, and bone production was present in the lesion of the upper lobe. Moreover, in addition to these 2 metastatic foci, the tissue of resection contained one area of dense fibroblastic activity with microscopic spicules of osteoid, and another area of alveolar tissue compressed by a nodule of bone formation. Since then, he remains free of recurrent disease at 10 years from his last metastasis.

Case IX. Patient L.B. This boy was found to have a large right intra-abdominal mass at age three months. Following admission to the Children's Hospital Medical Center, and diagnostic evaluation, he underwent laparotomy for removal of a left suprarenal neuroblastoma. At surgery, the liver was enlarged to the iliac crest due to massive tumor infiltration. Bone marrow aspirate, at this time, was positive for tumor infiltration; roentgenograms of the skeletal system showed no bone destruction. Post-

operatively, he received 1,540 rads in 21 to the entire abdomen to include the left su renal fossa and the entire liver. In addition received 0.4 mg./kg. body weight of nitr mustard in 2 evenly divided doses. One m following completion of this irradiation developed a firm mass overlying the frontal bone, associated with proptosis peri-orbital ecchymosis of the right eye. Re genograms of the skull now revealed a des tive lesion of the right frontal bone (Fig. He received 1,350 rads in 7 days to the e cranial vault on the assumption of mu sites of involvement. Vincristine (1.5 mg. and cytoxan (300 mg./m.2) were adminis on alternate weekly injections from this sion. At the end of another month, the over the right frontal bone had increase size and he became irritable. An addit 1.000 rads in 8 days was delivered to the 6 cranial vault. His irritability regressed right frontal mass remained unchanged. D this same time interval, his liver became ually less palpable (from 8 cm. below the costal margin at diagnosis to 3 cm. at this t He remained stable for the ensuing 3 m when he then developed left-sided seizur volving the left arm and left leg. At this he received an additional 700 rads in 5 da the local area of the right frontal mass. the next 3 months, or approximately 9 m following diagnosis, the right frontal

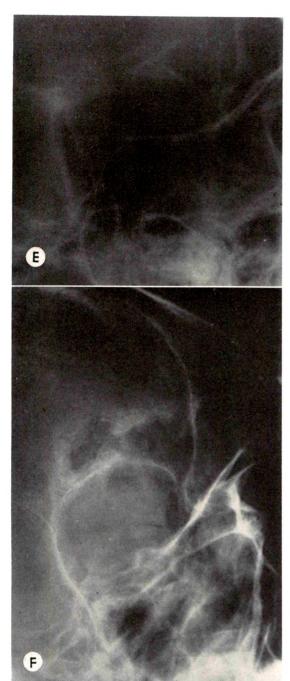


FIG. 6. (E) Oblique view of the right bony orbit 27 months later, at a time when he developed right proptosis and ptosis, reveals an osteolytic destructive lesion of the superior rim. (F) Four years later, following treatment with 6,000 rads and actinomycin D, there is reactive sclerosis to the superior margin of the bony orbit. He remains free of active disease since last metastases, or for the past 11 years.

proptosis and ecchymosis regressed, skull roentgenograms revealed the destructive lesion to be healing, his liver became nonpalpable, and his bone marrow was free of tumor cells on bone marrow aspiration. He continued on the vincristine and cytoxan regimen to a total of 28 months and has not received further treatment for the past 14 months. His skull roentgenograms now show complete healing of his destructive lesion (Fig. 8B) and he is free of all active disease at this time, or  $3\frac{1}{12}$  years since diagnosis.

#### DISCUSSION

It is beyond the scope of this report to evaluate the over-all long-term survival of children with the various malignancies described. No attempt is made to evaluate the over-all effectiveness of therapy in a large number of patients nor is a survival rate implied. Other reports from this Center have described such over-all results in Wilms' tumor and neuroblastoma. Future reports will detail such results for other types of malignancies in childhood and will evaluate the treatment regimen in relation to presenting symptoms and signs, extent of local tumor involvement and metastatic spread.

Rather, it is our wish only to emphasize that advanced, multiple, or recurrent metastases can be managed successfully under an approach which is both optimistic and rational.

Thus, in the management of Wilms' tumor metastatic to the lungs, we have preferred to treat both entire lung fields with irradiation of low dose (approximately 1,200 rads in 8 treatments) in combination with actinomycin D, even if only one focus of metastasis is evident by chest roentgenogram at the time of the first appearance of such metastasis. This is because we have noted that approximately 65 per cent of children with lung metastases from Wilms' tumor will have radiographic evidence of multiple and bilateral lung involvement. In truth, solitary metastases may occur. However, as in Case IV, it is unclear as to which patient has a truly solitary metastatic focus at the first manifestation of a

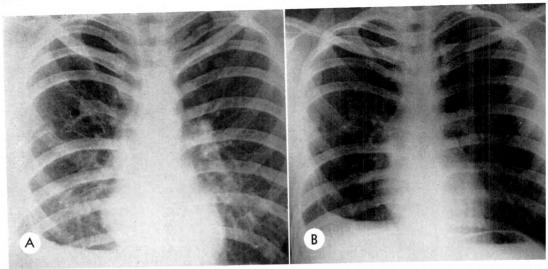


Fig. 7. Case VIII. (A) Posteroanterior chest roentgenogram, taken  $2\frac{1}{2}$  years from diagnosis of osteogenic coma, and 6 months following a right lower lobectomy for a solitary metastasis, shows a density in the u lobe and another at the left hilum of the left lung. (B) Following irradiation and mitomycin C, the less regressed completely for a period of 3 months, but then recurred. This roentgenogram, at 4 months lung irradiation, shows the recurrence in the left upper lung field. Shortly thereafter, the lesion at the hilum also recurred. Following thoracotomy and wedge resection of these 2 lesions, he has been frefurther metastases for the past 10 years.

lung metastasis. Therefore, we have preferred to assume the presence of multiple "microscopic" foci and to treat both lung fields in continuity. This allows us to avoid irradiating an adjacent area of lung parenchyma should an unsuspected focus arise therein, and thus avoids the danger of a "hot spot" at the juncture of 2 such portals. The relatively low dose of irradiation used in combination with actinomycin D has not caused obvious adverse effects on pulmonary tissue in later clinical follow-up evaluation, which includes pulmonary function tests performed in several patients. Indeed, even when such a course of bilateral lung irradiation is repeated at the doses described (as in Cases 1, 111 and 1v), we have noted no clinical or function test abnormality, at least as yet. Finally, the over-all effectiveness of this therapy (to be evaluated in greater detail in a separate communication), the lack of adverse reaction and the probability of multiplicity of lesions (Fig. 9, A and B), leads us to suggest this as the initial management of Wilms' tumor metastatic to the lungs. Surgical extirpation of solitary recurrent and/or

resistant lesions should be held in resibut used whenever so indicated.9

Our past experience with patients v neuroblastoma would agree with the perience of others that prognosis is rel to age of the patient at diagnosis, loca of the primary tumor and treatmen Although bone metastases by roentg graphic evaluation may indicate a hop prognosis, the outlook may be some more optimistic in a child under I yes age with this finding. Over all, the out of a child with bone metastasis, in this ease, is limited to only a few case rej in the literature.4 Nonetheless, the that such children have survived, espec in the younger age group, with bone tastases demonstrated roentgenogra ally, and the fact that the over-all ou is improved in the younger child even dissemination to other sites (such as liver), implies the rationale of opt tic pursuit in treatment. In terms of th of irradiation to such sites, it implies that relatively few such lesions are pre Such an approach, with "aggressive" diation of local bone metastases may

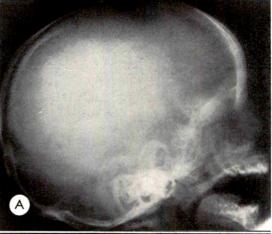
Fig. 8. Case IX. (A) A destructive lesion of the right frontal bone is visible 2 months following diagnosis of left suprarenal neuroblastoma, with metastases to liver and infiltration of bone marrow in this  $5\frac{1}{2}$  month old child. There is a soft tissue mass associated; there is reactive tumor bone formation. (B) Two years later, all evidence of metastatic disease has regressed. He has been free of disease for the past  $3\frac{1}{2}$  years.

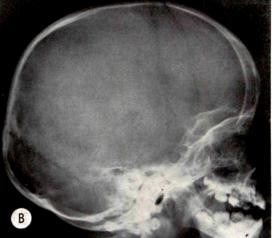
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less basis in the older child, who generally has evidence of more widespread dissemination to bones on roentgenograms.

The management of patients with Ewing's sarcoma, with irradiation, has been reported by others.<sup>5,8</sup> With sufficient dose, local control may well be expected. If, then, such local control of the primary lesion is possible, effective management, with irradiation, of a single metastatic focus likewise should be achieved. How often local single manifestations of metastases are evident in a large series of patients, however, will be the subject of a separate report.

The ability to control a primary undifferentiated rhabdomyosarcoma has been noted by others, when effective therapy,





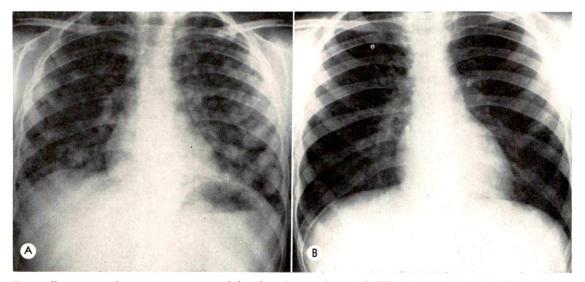


Fig. 9. Posteroanterior roentgenograms of the chest in a patient with Wilms' tumor show (A) the extensive involvement that may occur and (B) the response that may be expected with low dose bilateral lung irradiation and actinomycin D, as described in the text. Variations of this degree of dissemination have been seen in almost  $\frac{2}{3}$  of those patients with Wilms' tumor, metastatic to the lungs.

including irradiation, chemotherapy, and surgery, has been administered. Our over-all experience indicates a very guarded prognosis for patients with hematogeneous metastases. However, we have observed several patients, such as Case vi who have survived despite regional lymph node extension. The contribution of each modality, i.e., surgery, irradiation, and chemotherapy, is difficult to assess. In Case vi, at least, the control of residual tumor in the optic nerve and in the perimandibular region would indicate the effectiveness of irradiation and/or chemotherapy.

We shall not expand further, at this time, on the problem of metastatic osteogenic sarcoma. The over-all poor survival and the aggressive nature of metastatic disease have accounted for very few patients similar to Case VIII. It is our impression, however, that the chances of a lung metastasis being truly localized, and therefore eradicated by thoracotomy, are greater if such lesions do not appear within the first 2 years of original diagnosis.

We have not included other types of malignancy of childhood, such as the malignant testicular neoplasms in this discussion. This has been reported previously. As we noted at that time, involvement of regional lymph nodes and/or lung metastasis has been consistent with survival under persistent therapeutic management. Indeed, the survivals noted in that report are still apparent at this time, without further evidence of metastases in any patient.

#### SUMMARY

From the over-all experience of the Department of Radiation Therapy, Children's Hospital Medical Center, we have selected 9 patients with various types of malignancy.

In each case, a persistent approach to

metastatic disease, using irradiation modality, but also chemotherapy as gery, has achieved long-term surviv have not attempted to relate these is cases to our over-all results.

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# TITANIUM AS AN ENCASEMENT FOR COBALT 60 WITH SPECIAL REFERENCE TO A PNEUMATIC AFTERLOADING THERAPY UNIT

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COBALT 60 sources used in therapy are most often encased in stainless steel. This is relatively satisfactory for the powerful sources used in large cobalt therapy units, since large stainless steel encasements can be loaded with radioactive cobalt by remote control in a hot cell, but to load small sources in similar fashion is most difficult.

The purpose of this article is to introduce the use of titanium as an encasement for radioactive cobalt 60. This metal is light in weight, hard, tough and resistant to erosion. It becomes only slightly radioactive when properly bombarded by neutrons, and its isotopes have short half lives so its activity is soon dissipated. Such a modality is essential for encasing small cobalt 60 sources, which must be encased before irradiation. It is probable that titanium could well be used for all cobalt 60 sources.

Ralston Paterson<sup>7</sup> has stated in discussing the choice of technique of radiation therapy, "The radium applicator (mold) is in many senses the only ideal method in that when applicable it enabled radiation to be given without trauma to a zone of tissue almost exactly limited to the tumor bearing zone." He used relatively weak radium sources and left them in place for several days.

Frank É. Simpson<sup>8</sup> purchased one and a half grams of radium in 1917. Using strong applicators (200 to 1,000 mc radon) he developed a technique of high intensity, short daily treatments for accessible tumors. For the past 37 years one of us has employed this technique with excellent results.<sup>1</sup>

Since the handling of high dose rate radium applicators is not feasible in most clinical departments, we have designed and developed a remote controlled unit called the "Pneumatron" for the afterloading of radioactive cobalt sources from a reservoir to a prearranged applicator.<sup>2</sup> This unit is now in service.

Realizing the logic of high intensity short distance therapy, Joslin, O'Connell and Howard<sup>3</sup> of the Charing Cross Group of Hospitals, London, have also devised a remote control afterloading unit called the "Cathetron" in which powerful cobalt 60 sources are inserted in preadjusted applicators by means of a long cable. Most of their clinical work has been with cervical cancer.

Liversage, Martin-Smith and Ramsey, also of the Charing Cross Group, have made exhaustive studies on the physical measurements of the "Cathetron" sources. Their sources consist of a number of stainless steel cylinders each about 1½ cm. in length and each containing one or more curies of cobalt 60. Steel becomes radioactive when placed in a pile, so it is obvious that these cylinders must be loaded in a hot cell.

Since it is difficult to transfer a cylinder pneumatically, we use titanium spheres with a small amount of cobalt 60 in the center. The spheres,\* 1/8 inch in diameter, are drilled and loaded with 1 cu. mm. of cobalt which has been plated with nickel. This plating provides one seal. The drilled hole is then welded shut and the titanium provides the second seal required by the

<sup>\*</sup> Round sources were suggested to the senior author by Herbert M. Parker, Ph.D.

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United States Atomic Energy Commission. The balls are then placed in the pile and irradiated until the cobalt has attained its desired strength. The experimental model of the Pneumatron contains 9 such sources, which, when loaded into an applicator, provide a linear source 11 inches long with a total strength of 1 curie of cobalt 60.

The advantages of the divided dose, high intensity, proximity (short distance) therapy in the treatment of accessible tumors has been proven through long experience.<sup>2</sup> It is particularly useful in cancer of the mouth, uterus, skin and for irradiation of the chest wall following mastectomy or recurrent breast cancer. In any case, it is possible to deliver a massive dose to a tumor without injury to the underlying or adjacent tissues.

The Pneumatron, by permitting remote control of high intensity proximity therapy, makes this type of treatment available for busy radiation centers in which the manual handling of powerful radium or cobalt applicators is impossible.

Since the cost of medical care is becoming a most dominant factor, it should be noted that the Pneumatron will be relatively inexpensive and treatment is nearly always on an out-patient basis, thereby eliminating expensive hospitalization.

#### PHYSICAL PROPERTIES OF TITANIUM

Titanium belongs to the family of refractory metals. Because of its excellent physical properties; i.e., mechanical strength, melting point, weight, and corrosion resistance, this metal, in either pure or alloy forms, has been widely used in the aircraft and aerospace industries for many years. Titanium provides excellent resistance to most corrosive substances. This is the result of the formation of a protective film of stable oxide or absorbed oxygen. In many ways, titanium is more resistant to corrosion than stainless steel. It is resistant to acids and to chloride salts. However, it is attacked readily by concentrated sulfuric and hydrochloric acids.

Titanium is a relatively light metal with a density of 4.51 gm./cm.8, which is about 40 per cent less than that of steel and about 75 per cent more than that of aluminum. It has a hardness of about 80-150 vickers, and electrical conductivity equal to 3.6 per cent of that of copper, and a specific heat of 0.13 cal./gm./°C. The melting temperature of titanium is about 1,660° C., which is somewhat higher than that of stainless steel. Its mechanical strength drops rather rapidly at temperatures above 500° C. Table I lists some of the physical properties of titanium metal as compared with that of #304 stainless steel and pure aluminum.

#### NUCLEAR PROPERTIES OF TITANIUM

The element titanium has 5 stable isotopes of varying degrees of abundance. Their mass numbers range consecutively from 46 to 50. Although the element has radioactive isotopes, the only significant one is  $T_{122}^{151}$  which is produced by  $T_{122}^{151}$  (n,  $\gamma$ )  $T_{122}^{151}$  reaction when a neutron is captured by  $T_{122}^{150}$ .  $T_{122}^{151}$  decays very rapidly into  $V_{23}^{51}$  with a half life of only 5.79 minutes. All the 4 other stable isotopes of titanium result in stable isotopes in neutron capture reaction. Table 11 shows the relative abundance and activation cross sections of the 5 stable isotopes of titanium.

Besides the radiating capture reactions described above, 2 other processes involving titanium isotopes are the (n, p) and the  $(n, \alpha)$  reactions. Table III gives the cross section values and the threshold energies of these reactions.

Due to the minute probability for the occurrence of the  $(n, \alpha)$  reactions, we shall neglect the contribution from them. The most troublesome process involving the neutron bombardment of titanium isotopes is the formation of  $Sc_{21}^{46}$  by the (n, p) reaction. Radioactive  $Sc_{21}^{46}$  returns to stable  $Ti_{22}^{46}$  with the emission of a beta particle; the decay half life of 84.1 days is long enough to be the only drawback in this method of using titanium isotopes for encapsulation. Radioactive  $Sc_{21}^{47}$  from

Table I SOME PHYSICAL PROPERTIES OF Ti, Al and 304SS

	Ti	Al	304 Stainless Steel
Density (gm./cm.³) Melting point, °F. Boiling point Hardness (vickers) Tensile strength (psi)	4.5 2,982 3,260° C. 74~94 126,000	2.7 1,220 2,452° F. 12-25 10,000	7.9 2.550 150 85.000

the  $Ti_{22}^{47}$  (n, p)  $Sc_{21}^{47}$  reaction emits gamma rays ( $E\alpha = 0.16$  mev.) with a half life of 3.43 days. Due to the low gamma energy and relatively fast decay,  $Sc_{21}^{47}$  does not possess great problems for our purpose. The low energy gamma rays can be shielded easily and a waiting period of approximately I month is all that is needed to avoid this complication. Owing to the high threshold energy and the small cross section, the formation of  $Sc_{21}^{48}$  can be kept below exemption level. Some properties of these Sc nuclei are given in Table IV.

The way to get around the interference from Ti<sup>46</sup><sub>22</sub> (n, p) Sc<sup>46</sup><sub>21</sub> reaction (which has an effective threshold energy of 1.61 mev., including contributions from barrier penetration) is to choose an appropriate irradiation location inside a nuclear facility or reactor, where the energies of fast neutrons have been appreciably downgraded by slowing down and moderation. The calculation indicates that the criterion for

this selection should be based upon a ratio of thermal to fast neutron fluxes greater than 10<sup>4</sup>. This restriction can be met conveniently in the reflector or moderator regions of high power or high flux reactors. However, for small reactors with low central peak neutron intensity, the source irradiation time may become excessively long.

When the Pneumatron is released for distribution, the plan is to provide a unit with 50 balls containing a total of 5 curies of cobalt 60. The machine will be so constructed that the operator can withdraw 10, 20, or the entire 50 balls for afterloading different sized applicators. Ten ball applicators would be specifically useful for cervical and intraoral cancer. The 20 ball unit for an intrauterine applicator and for treatment of moderate sized skin cancers. The 50 ball applicator measuring 6 inches in length would be specifically use-

TABLE II

PER CENT ABUNDANCE AND ACTIVATION CROSS
SECTION OF STABLE TITANIUM ISOTOPES

Isotope	Per Cent Abundance	σ (barns)
$Ti_{22}^{46}$	7.93	0.6
Ti <sub>22</sub> <sup>47</sup>	7.28	1.7
${ m Ti}_{22}^{48}$	73.94	8.0
$T_{122}^{(4')}$	5 · 5 I	1.93
${ m Ti}_{22}^{50}$	5 · 34	0.14

Table III

cross sections and threshold energies of the (n, p) and  $(n, \alpha)$  reactions

Reactions	σ (barns)	E Threshold (mev.)
Ti <sub>22</sub> (n, p) Sc <sub>21</sub> <sup>46</sup>	4.1×10 <sup>-3</sup>	1.61
$T_{122}^{47}$ (n, p) $Sc_{21}^{47}$	0.2×10 <sup>-3</sup>	-0.096
$Ti_{22}^{48}$ (n, p) $Sc_{21}^{48}$	0.077×10 <sup>-3</sup>	3.28
$T_{122}^{148} (n, \alpha) Ca_{20}^{45}$	5.5×10 <sup>-6</sup>	2.02
$Ti_{22}^{50}$ (n, $\alpha$ ) $Ca_{20}^{47}$	2×10 <sup>-7</sup>	3.58

Table IV

HALF LIFE AND MODE OF DECAY OF SOME
SCANDIUM ISOTOPES

Isotopes	t½ (days)	Decay Mode (E in mev.)
Sc21	84.1	$\beta = 0.36 \text{ (max.)}$ $\gamma = 1.12, 0.89$
Sc21	3.43	$\beta = 0.60 \text{ (max.)}$ $\gamma = 0.160$
Sc21 -	1.83	$\beta$ =0.65 (max.) $\gamma$ =0.175, 0.983

ful for large skin cancers or for chest wall irradiation.

#### SUMMARY

Titanium provides an ideal encasement for radioactive cobalt 60. Sources may be encased before being irradiated in the pile since the small amount of radioactivity induced in the titanium is soon dissipated due to its short half life. Titanium is hard, tough, chemically resistant and very light in weight.

It is being used in a new afterloading remote controlled unit called the Pneumatron in the form of small ball-bearings, 1/8 inch in diameter with 1 cu. mm. of radioactive cobalt 60 in the center. Several such balls are transferred through a plastic tube by pneumatic pressure from a storage container to a prefixed applicator. The average treatment time is from 2 to 5 minutes, following which the radioactive

balls are returned to the storage container also by pneumatic pressure.

This mechanism makes possible the high intensity proximity therapy of accessible tumors. It is particularly useful in the treatment of cancers of the skin, lips, mouth, cervix and for irradiation of the chest wall in patients with cancer of the breast.

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# A NEW DOSE CALIBRATOR FOR NUCLEAR MEDICINE\*

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WITH the increasing use of generators for the daily production of short-lived radionuclides such as 99mTc and 113mIn, the burden of responsibility for assay of these radiopharmaceuticals has shifted from the manufacturer to individual users. Two methods of assay are now in wide use: (1) dilution technique; and (2) ionization chamber technique for bulk assay. Dilution techniques are time-consuming, ionization chamber methods are simpler and more accurate. The ionization chamber instrument described in this paper is simple, accurate and relatively inexpensive (Fig. 1).\*

\* Model Mark IV. RADX Corporation, Houston, Texas.



Fig. 1. Nuclide dose calibrator.

- 1. Module for 99mTc (14 others commercially available).
- 2. On-off switch.

#### MATERIAL AND METHOD

The detector consists of 3 lucite cylinders (rendered electrically conductive by means of conducting paint) arranged as shown in

- 3, and 4. Push switches (cancel one another).
- 5, 6, 7, and 8. Meter range switches (cancel one another).
- 9. "Volume" potentiometer.
- 10. "Dose" potentiometer.
- 11. Light spot of microammeter.
- Upper scale of microammeter (indicates activity).
- 13. Lower scale of microammeter (indicates volume to be administered).
- 14. "Zero adjust" potentiometer.
- 15. Measuring well.

Zero Adjustment: With power on and switches 4 and 7 closed, potentiometer 14 is adjusted to bring the light spot to zero on the scale.

Activity Measurement: Switch 5 is closed (canceling 7) and a flask containing elution (for example 30 cc.<sup>99m</sup>Tc) is placed in the well. If deflection is below 30 millicuries, switch 6 is substituted for switch 5, etc. The reading on the upper scale is the activity of the elution. Location of the decimal point is determined by the particular switch (5, 6, 7 or 8) employed.

Dose Volume Calculation: Switch 3 is closed (canceling 4). Potentiometer 9 is set for the cc. of elution in the well and potentiometer 10 for the dose in millicuries that is to be delivered. Now the light spot shows on the lower scale the number of cc. necessary to provide the desired dose.

Checking Dose in Syringe: As a further check the syringe containing elution for injection can be placed in the well and switch 4 closed (canceling 3). The reading on the upper scale shows the activity of the material in the syringe.

Radium Standard: A convenient means of checking of the system is to employ a <sup>226</sup>Ra module and a standard radium source. With such a module in place, the standard in the well and switch 4 closed, the upper scale reading is the activity of the sample. Discrepancy between such a reading and the known activity of the radium standard requires the services of a physicist or a service representative.

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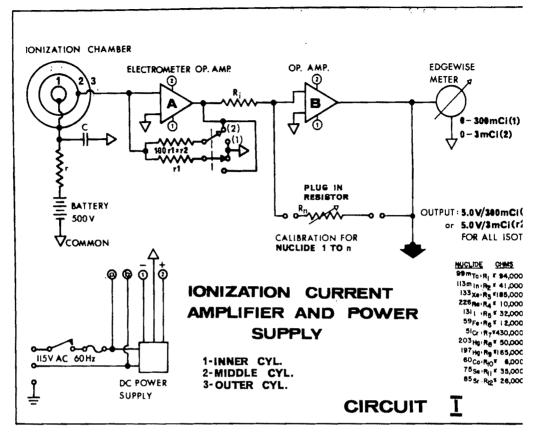


Fig. 2. Circuit I-the basic measuring circuit.

Figure 2. The inner cylinder (1) which serves as the measuring well is thinner than the others to minimize attenuation of low energy gamma emitters such as 99mTc and is in electrical contact with the outer cylinder (3). The middle cylinder (2) serves as the collecting or sensitive electrode and by means of a long stand-off terminal connects to the input of electrometer amplifier A. The cylinder assembly is strengthened and made rigid and air-tight by lucite plates at top and bottom. The polarizing voltage for the chamber is obtained from a 500 volt dry cell battery. The chamber response with respect to the volume of solution to be assayed is approximately ± 1 per cent for volumes ranging from 2 ml. to 35 ml.

The circuit shown in Figure 2 is used for initial amplification of the ionization current. The signal current from the ionization chamber is fed to the input of an operational

electrometer amplifier A. The output from amplifier A (maximum approsonous) is the voltage across of resistors ri or ri. Because of the hiloop gain of the amplifier, the foresistors can be switched on the side of the amplifier thus eliminated for a special high insulation structure. The error introduced by conthe output side of ri or rize to groun than removing the resistor from the can be neglected so long as

$$\frac{r^2}{G \times rI} \ll I.$$

(G=open loop gain which is about to 100,000.)

The output from amplifier A is co to the input of operational amplifier feedback resistor modules R<sub>I</sub> to used for measuring the various radionuclides to be assayed. The module for each radionuclide has been adjusted so that 300 mCi produces an output signal of 5.0 volts. Typical resistor module values are listed in Figure 2.\* A meter connected to the output of amplifier B measures activity. Amplifier B also provides a low output impedance source necessary for the "ratio" circuitry. Figure 2 represents the basic measuring circuit for determination of activity (mCi) and Figure 3 the simpler of 2 methods for automatically calculating the volume of nuclide to be administered to a patient.

The output voltage of the circuit in Figure 2 is integrated by amplifier C. The output of this amplifier is fed to a voltage comparator D. As long as this voltage is less negative than the voltage from potentiometer P1 (volume adjustment) the field effect transistor (FET) is conducting. As soon as the 2 voltages are equal, the output voltage of the comparator amplifier swings from a high positive voltage to a high negative voltage which causes the FET to become virtually non-conducting. The integration of the voltage from P2 (activity to be administered) by amplifier E is thus interrupted. It can be shown that the output of amplifier E is proportional to the volume to be administered and the meter can therefore be calibrated to read directly in cubic centimeters. There are, of course, other methods of obtaining the ratio electrically and miniature-sized dividing and multiplying modules are widely available.

The principal advantages of the instrument are: (1) rapid response of the detector (several seconds) which reduces radiation

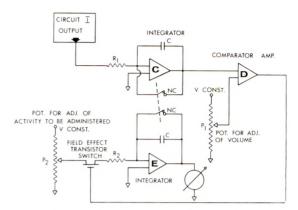


Fig. 3. Circuitry used in conjunction with Circuit I to obtain and display the volume of liquid to be administered to the patient.

exposure of the technician; (2) automatic calculation of the volume of liquid to be injected into the patient which reduces possible human errors; and (3) use of plugin modules for the different radionuclides which avoids the need for purchase of standards and individual calibration in every nuclear medicine laboratory when new radionuclides are introduced in the future.

#### SUMMARY

An ionization chamber dose calibrator for bulk assay of millicurie levels of radio-activity and the automatic calculation of the volume of nuclide to be administered are described. Two versions are offered, a less expensive one with analog readout and a more expensive version with digital readout. In both versions the design of chamber and circuits obviates the necessity of any calculation at all by the technician.

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<sup>\*</sup> R1 to Rn values are influenced by ionization chamber design and other structural details. Those listed are for the commercial unit (Fig. 1). For a custom built instrument the values would have to be determined experimentally.

# CLINICAL EVALUATION OF A NEW PORTABLI UNIT RADIOGRAPHIC TECHNIQUE\*

By KENNETH R. WING, D.M.D.,† RUNE SÖREMARK, D.M.D., O.D.,† and BENGT HULTING, M.D.,‡ NYKÖPING, SWEDEN

THE possibility of using radionuclide ■ sources of x rays and/or low energy gamma rays for radiography was first demonstrated in 1948 by Spangenberg. 18 It was immediately obvious that their independence from electrical power would make these sources truly portable and their small size would make possible new positioning techniques with the source placed within body cavities.18 Much of the early interest centered on thulium 170, but further investigation revealed its impracticality due to the presence of hard beta radiation resulting in bremsstrahlung which reduces the contrast in the radiographs and increases the shielding requirements. 4,6,11,16

Several comprehensive investigations of the suitability of available radionuclides as sources of radiation for radiography have been made. 10,14,15,17 Iodine 125 has been recognized as being one of the more promising sources. The radiation is predominantly 27 to 32 kev. x rays with small contributions of secondary x rays from the source material and unconverted 35 kev. gamma rays.1,2,15 This radiation is theoretically ideally suited to radiographic examination of the jaws and teeth and the smaller skeleton of the extremities. Radiographs of good contrast and detail have been made of the hand and the jaws. Panoramic radiographs of the teeth have been made with the source placed intraorally.1,8

Robbins and Land<sup>15</sup> first used Polaroid 3000X 10×12 inch Land films with an intensifying screen for radiography in 1951. This low dosage technique has been successfully applied to radiography in the operating room and in other situations in which

rapid film processing is of advantage Polaroid 4×5 inch Land films have been used with intensifying and scopic screens for radiography with results. 7.18 While the 10×12 inch fil quire a large, electrically operate processor, the 4×5 inch films require the hand operated Polaroid XR-7 cassette for exposure and initiation development and are therefore easily able.

Combination of a radionuclide with the Polaroid Land technique provide a truly portable radiograph. A pilot study has demonstrated the bility of combining an iodine 125 ra source (Soremark X-ray Unit) with roid 4×5 inch Land films in a P XR-7 Land cassette with an intensif fluoroscopic screen. The object present investigation was to asser portable radiographic units employiodine 125 source and the Polaroid technique and to critically evaluate effectiveness of these units as dia instruments.

#### MATERIALS AND METHODS

Two portable radiographic unit been assembled. The larger of the 2 consists of a radionuclide source (So X-ray Unit), Polaroid 4×5 inch Lar in a Polaroid XR-7 Land cassette ec with an intensifying or fluoroscopic and an examination table with hold both the source and cassette. The unit, exclusive of films and the source port shield, weighs approximately and requires a space 20×30 cm. The

The Swedish Atomic Energy Company, Studsvik, Nyköping, Sweden, supplied the Soremark X-ray Unit. Films and cassettes were provided by Polaroid Corporation, Cambridge, Massachusetts, U.S.A.

<sup>\*</sup> From the Swedish Research Council's Laboratory, Studsvik, Nyköping,† and the Radiology Department, Nyköpin Nyköping,‡ Sweden. This investigation was supported in part by U.S. Public Health Service Post-Doctoral Fellowship 2 610-03 from the National Institute of Dental Research.

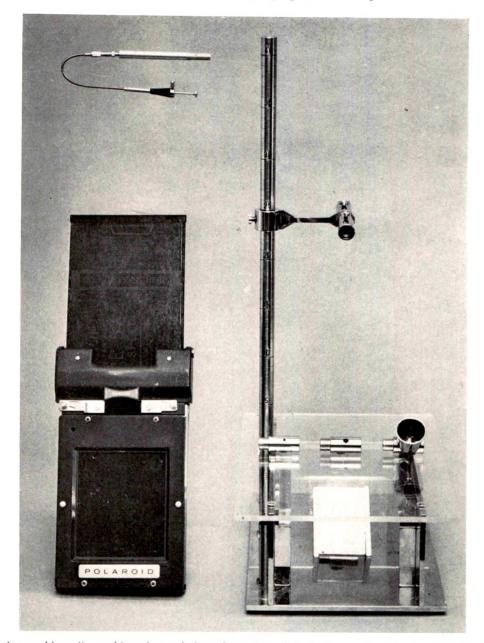


Fig. 1. A portable radiographic unit consisting of a radionuclide (iodine 125) source (upper left), Polaroid 4×5 inch Land film in a Polaroid XR-7 Land cassette equipped with an intensifying or fluoroscopic screen (lower left), and a small examination table. A single Type 57 film packet is in place in the cassette and ready for exposure. The table has a cassette holder and an adjustable source holder with interchangeable columnators. The unit is seen in use in Figure 3.

top is 10 cm. high and the removable support for the source holder is 50 cm. long.

The smaller radiographic unit (Fig. 2) is much simpler in design. The source holder is fixed directly to a Polaroid series 100 Land camera back at a focus film dis-

tance of 15 cm. An intensifying or fluoroscopic screen is mounted on the inside of the light shield for the front of the camera back—a modification suggested by a similar one of Howieson and Higgins.<sup>9</sup> An 8 film pack of Polaroid 3 1/4 × 4 1/4 inch



Fig. 2. A portable radiographic unit consisting of the source and a source holder which is fixed directly to a modified Polaroid series 100 camera back. An intensifying or fluoroscopic screen is mounted on the inside of the light shield facing the film. An 8 film pack of Polaroid Type 107  $3\frac{1}{4} \times 4\frac{1}{2}$  inch Land films is in place in the camera back. The source film distance is fixed at 15 cm. The unit is seen in use in Figure 3.

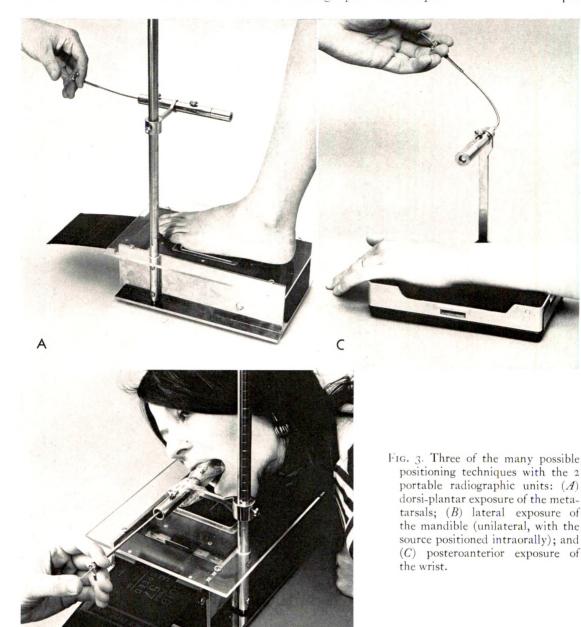
Land films is used in the series 100 camera back. This unit weighs approximately 1 kg.

The radiation source has been described in detail elsewhere.<sup>2,3,8</sup> The radionuclide used in this source is iodine 125 (I<sup>125</sup>). The source used in the present investigation contained 300 mc at the outset. The source (focus) is less than 0.5 mm. in diameter and is enclosed in a welded titanium capsule. A capsule shutter release cable is used to move the sealed source from behind its tantalum

radiation shield into the exposure position. An internal spring returns the source its shielded position. The radiation emit by this source, predominantly 22 to 35 ke has a first half value layer in aluminium approximately 1.8 mm. and produces rac graphs with a contrast scale which is comparable to that produced by a convention roentgen ray tube running at approximat 50 kvp.

In Figure 3, A-C, the 2 units are sho assembled and 3 positioning possibilities demonstrated. Exposures may be tirusing any clock with a sweep second ha Removing the exposed film from the X cassette or the series 100 camera back tiates the developing process. A black white, positive print is ready for viewin 15 seconds. The cassette or camera have be used immediately for a new er sure.

Test exposures with aluminum and per penetrometers as the objects were n using Polaroid Types 57 (ASA 3000) 52 (ASA 400) Land films in an XR-7 sette with Du Pont CB-2 Fluorosco Lightning Special, High Speed, Par S and Detail Combination screens in c to obtain relative exposure times with different film-screen combinations. Ra graphs of the fingers, thumb, hand, w forearm toes and foot of normal individ were made with the faster film-screen binations in order to determine the pr exposure times and their variations. I a calibrated ionization chamber, the rates at various distances from the so in its exposure position were measured. skin doses incurred in making exposur the wrist in the posteroanterior pos with the portable radiographic unit Type 57 film and a Lightning St screen and with a conventional roei ray tube and Kodak Kodirex film were determined. Using the portable units the faster film-screen combinations, 1 graphs were made of a series of 20 pa in whom fractures of the smaller bor the extremities had been demonstrat conventional roentgenograms.



RESULTS

Type 57 film with a CB-2 Fluoroscopic screen was shown to be the fastest combination. Type 57 film with a Lightning Special screen is 4 times slower. Both the High Speed and Par Speed screens with Type 57 film require 16 times the exposure for the CB-2 Fluoroscopic screen. The com-

binations with Type 52 film require 8 to 10 times the exposures for the corresponding combinations with Type 57 film. The exposure times using Type 57 film and a Lightning Special screen with the 300 mc source ranged from 6 seconds for an adult finger in the posteroanterior projection to  $1\frac{1}{2}$  minutes for an adult forearm in the



Fig. 4. A lateral radiograph of the left thumb with a chondroma and a healing fracture (arrows) of the first metacarpal. Technical factors: 300 mc iodine 125; 12 seconds; 15 cm. focus film distance; Type 57 film; Lightning Special screen.

lateral position. Thus, the only combinations with reasonable exposure times were the CB-2 Fluoroscopic and Lightning Special screens with Type 57 film (Type 107 film for the series 100 camera back).

The dose from the source in its exposure position fixed in the source holder with a proper columnator was 290 mr·min.<sup>-1</sup> at 4 cm., 37 mr·min.<sup>-1</sup> at 10 cm. and 6.4 mr·min.<sup>-1</sup> at 25 cm. As these measured doses conform well to the "inverse-square" law, the dose may be expressed as 14 mr·cm.<sup>2</sup>·min.<sup>-1</sup>·mc<sup>-1</sup>. Two techniques for making radiographs of the wrist in the posteroanterior projection were compared with regard to the dose incurred in making comparable radiographs. In the first, the radionuclide source was used with Type 57 film in an XR-7 cassette with a Lightning Special screen at a focus film distance of

15 cm. In the second, a conventional roentgen ray tube with 1 mm. additional Al filtration running at 45 kvp. was used with Kodak Kodirex film (no screen) at a focus film distance of 70 cm. The doses measured at skin level, 10 and 65 cm. respectively, were 13 mr for the portable unit technique and 385 mr (7.7 mr·mas.<sup>-1</sup>) for the conventional roentgenographic technique.

In Figures 4 through 7 appear radiographs of 4 of the patients with fractures of the smaller skeleton of the extremities. Each of the 4 radiographs was made using one of the portable units with either Type 57 or Type 107 film and a Lightning Special screen. Using the iodine 125 decay curve, the exposure times for the radiographs have been normalized to the time of receipt of the source, at which time it contained 300 mc iodine 125. These radiographs are rep-



Fig. 5. A posteroanterior radiograph of the third finger, left hand, with a fracture (arrow) of the middle phalanx. Technical factors: 300 mc iodine 125; 6 seconds; 15 cm. focus film distance; Type 107 film; Lightning Special screen.

resentative of the best of those obtained in this investigation. A comparison of the radiographs obtained using the portable unit technique with the original, conventional roentgenograms showed a marked difference in both contrast and definition in favor of the conventional roentgenogram (no screen medical film; 70 cm. focus film distance; 45-50 kvp.). In particular, fractures in which little or no dislocation of the bone fragments occurred were difficult to impossible to demonstrate with the portable unit technique. In several cases, blurring occurred due to subject movement during the long exposure times with the portable unit. Radiographs made with the CB-2 Fluoroscopic screen were of such low resolution that they could not be used for fracture diagnosis.

#### DISCUSSION

Iodine 125 is now available carrier-free in curie quantities at relatively low cost.

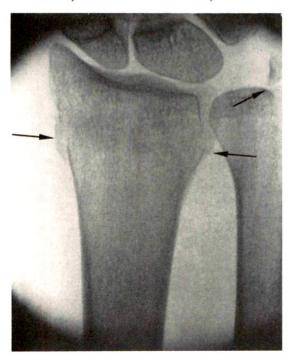


Fig. 6. A posteroanterior radiograph of the right wrist with a fracture through the distal end of the radius (arrows) and avulsion of the styloid process of the ulna (arrow). Technical factors: 300 mc iodine 125; 25 seconds; 15 cm. focus film distance; Type 57 film; Lightning Special screen.

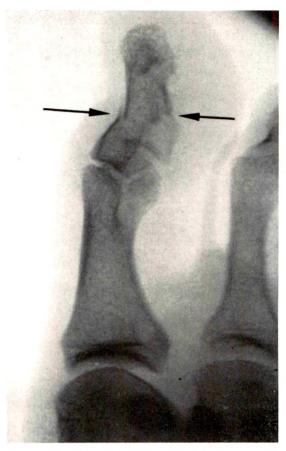


Fig. 7. A lateral radiograph of the right big toe with fracture (arrows) through the base of the distal phalanx. Technical factors: 300 mc iodine 125; 10 seconds; 15 cm. focus film distance; Type 57 film; Lightning Special screen.

Sources of up to 500 mc can be made with a diameter (focus) of less than 0.5 mm. The 60 day half life of iodine 125 represents a good compromise between the conflicting demands on such a source that it have a long useful lifetime and that it also have a high output from a small focus. With the exception of the low energy L rays and Auger electrons which can easily be filtered out, all of the radiation emitted in the disintegration of iodine 125 is useful for radiography. The relative yield of iodine 125 is very high with approximately 140 useful rays being emitted for every 100 disintegrations. The source used in the present investigation was prepared as silver iodide and, therefore, a small portion of the emitted

radiation is 22 kev. secondary K x rays from the silver. 2,8,8

The Du Pont Lightning Special screen, which was selected as the best compromise with regard to image quality and exposure time, is an intensifying screen of high speed type (barium lead sulfate) which is especially sensitive to low energy x and  $\gamma$ radiation. Polaroid Types 57 and 107 Land films are panchromatic and can therefore be used effectively with all intensifying or fluoroscopic screens regardless of emission characteristics. The use of the Lightning Special screen with Types 57 and 107 films results in an intensification of approximately 150 times, or a sensitivity approximately 50 times that of Kodak Kodirex film (no screen), with radiation of the quality emitted by the iodine 125 source.

This marked intensification is obtained at the expense of contrast and resolution in the radiograph (Fig. 4-7). The image quality is such that so-called hair-line fractures and all but the more extreme pathologic changes in bone (e.g., Fig. 4) will most likely go undetected. Despite this intensification, the exposure times with a 300 mc source are relatively long. With time, exposure times must be increased in order to compensate for the loss of activity due to decay of the radionuclide. With iodine 125, the exposure times must be doubled every 60 days. Due to the long exposure times, blurring of the radiographs due to subject movement is a problem with this technique despite the fact that the examination table could easily be placed in such a way as to provide the most comfortable position for the patient and that sand bags were used to assist the patient in holding still. As the source diameter is as large, the focus film distance as small, and the film-screen combination as fast as the demands on the image quality will allow, exposure times can be reduced or the use of slower film-screen combinations can be made possible only by using stronger sources. Due to the limitation which selfabsorption (attenuation of the radiation within the source) places upon the source

thickness, a practical limit for the strength of sources 0.5 mm. in diameter or less is approximately 500-600 mc iodine 125, or less than twice the strength of the source used in the present investigation.

While extensive use of these portable radiographic units is precluded by these limitations, they should most certainly find use in situations in which diagnosis would otherwise be extremely cumbersome or even impossible. Their use in the operating room under anesthesia and in the fields of forensic medicine and materials inspection is not limited, as exposure times of several minutes or more can easily be tolerated. Limitations of the use of these units on the basis of dose incurred by the patient are of minor importance as exposures 20 to 30 times those used in the present investigation can be made without exceeding the dose incurred during a conventional roentgenographic examination.

#### SUMMARY '

Two new portable radiographic units employing a radionuclide (iodine 125) source and Polaroid Land films with an intensifying or fluoroscopic screen were assembled and evaluated clinically.

The units are small, light in weight, simple to operate and completely independent of both electrical power and darkroom facilities.

The energy of the radiation emitted by the source, predominantly 22 to 35 kev., is best suited to the examination of the hand, wrist, forearm, foot, jaws (unilateral) and foreign bodies or calcifications in soft tissue masses.

Of the film-screen combinations tested, Polaroid Types 57 or 107 Land films with a Du Pont Lightning Special intensifying screen were chosen as the best compromise of the conflicting demands for good image quality and reasonable exposure times with a source of limited output.

The skin dose incurred by the subject with the portable units is less than 4 per cent of that for making comparable roent-

genograms with a conventional roentgen ray tube and Kodak Kodirex film.

While many common types of fractures can be detected using the portable radiographic unit technique, the limit of the diagnostic usefulness of these radiographs lies short of the demonstration of fractures in which little or no displacement of the fragments has occurred. Blurring due to subject movement is also a problem as the exposure times are relatively long and must be increased with time to compensate for the decay of the radionuclide.

Despite these limitations, these portable units should be quite useful in situations in which radiographic diagnosis would otherwise be impossible and, in addition, in the fields of forensic medicine and materials inspection, where exposure times of several minutes or more can easily be tolerated.

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#### m E D I T O R I A L S m

# OVARIAN CANCER WITH SPECIAL REGARD TO RADIOTHERAPY\*

OPINIONS differ concerning the value of irradiation as a useful adjuvant to surgery in the treatment of ovarian carcinoma. Surgery appears to deserve its position as the keystone in the treatment of ovarian malignant tumors in all stages. It is necessary that, at laparotomy, the surgeon outline in detail the disease. He should take multiple biopsies from areas suspicious of being involved by the growth.

The majority of clinicians agree that radiation therapy is of value in the palliation of ovarian cancer, subjectively and objectively, in particular when the disease is localized to the true pelvis. Some gynecologists believe that radiotherapy, in addition to surgery, will improve the results, while others question the value of irradiation in prolonging life.

Any attempt to analyze critically the reports in the literature on the value of radiotherapy is met with difficulty. Ovarian carcinoma is not an entity, and accurate comparison of therapeutic results cannot be made, unless the clinician takes into consideration the histologic type of the ovarian neoplasm.

The International Federation of Gynecologists and Obstetricians and the WHO have proposed a histopathologic classification of the ovarian neoplasms. This classification distinguishes germ cell tumors, teratomas, and hormone producing mesenchymal tumors as well as Brenner tumor and metastatic tumors from true ovarian epithelial tumors. Unfortunately, many clinicians include such tumors in the series of ovarian carcinomas.

Dysgerminoma. This is a comparatively rare tumor which appears in young women. Pedowitz and Felmers have collected a large series of cases treated by hysterectomy and bilateral salpingo-oophorectomy. They present a 5 year cure rate of 33.3 per cent. At the Radiumhemmet we have chosen a combined treatment of surgery and irradiation to the area of the growth and the retroperitoneal lymph nodes. It is desirable that a careful examination of the whole abdomen be carried out at laparotomy. A lymphography may give additional information. The dysgerminoma is a radiosensitive tumor. As a rule, it is not necessary to exceed a dose of 2,000 rads given within 3 weeks. It is true that involvement of both ovaries occurs in 10 per cent of the cases. In our opinion, the psychologic factor should be taken into consideration as the great majority of patients are less than 30 years of age. Therefore, we avoid irradiation of the normal ovary left in situ. In order to decrease the radiation dose to the normal ovary, it is necessary to give superor megavoltage irradiation. At Radiumhemmet, 64 cases of dysgerminoma have been treated prior to 1963. The 5 year cure rate amounts to 67.2 per cent. Six of 15 patients with extrapelvic extensive metastases are free from disease.

Granulosa cell tumor. This tumor has a potential degree of malignancy. Recurrences may appear first 10–20 years following surgical removal. Recurrences are more frequently seen in cases of sarcomatoid granulosa cell tumors than in those of cylindroid or folliculoid types. We consider it

<sup>\*</sup> Presented by title at the Fifty-second-Annual Meeting of the American Radium Society, Coronado Island, San Diego, California, March 1-5, 1970.

important to treat a sarcomatoid granulosa cell tumor as an ovarian cancer. Therefore, radiation should be given in addition to surgery in all cases of sarcomatoid tumors. In cases of cylindroid and folliculoid granulosa cell tumors it is questionable whether irradiation is of any value. However, in cases of recurrent tumors, preoperative irradiation with a dose of 3,000 rads will facilitate the surgical removal of the recurrent growth.

Epithelial ovarian tumors. Experience has shown that from a prognostic and therapeutic point of view it is essential to separate tumors of low potential malignancy from obvious carcinomas, although the former neoplasms clinically behave as a carcinoma, give rise to metastases and ascites and may cause the death of the patient. As a rule, clinicians do not distinguish between these two categories of malignant epithelial tumors. The author does not intend to discuss the histopathologic aspects; however, for pathologists, attention should be called to the fact that it is not difficult to keep tumors of low potential malignancy separate from obvious carcinomas, destructively involving the connective tissue of the growth. The clinical course, prognosis and treatment are quite different in cases of low potential malignant tumors from those of an obvious carcinoma. It is necessary to point out that the surgeon should send the whole tumor to the pathologist and not only pieces of the growth. This will facilitate an exact diagnosis. In the series of 925 cases of malignant ovarian tumors seen at the Radiumhemmet in the years 1958-1962, the tumor was of low potential malignancy in 158 cases; i.e., 17.1 per cent. The treatment has been surgery. Radiation has been administered with orthovoltage therapy, at least in all cases with metastases in the pelvis or above the pelvis. The 5 year cure rate in all cases of low potential malignant tumors amounts to 85 per cent.

A 5 year cure rate of more than 60 per cent has been achieved in 28 cases with extrapelvic metastases. The metastases in

cases of low potential malignant t grow superficially and have a good supply. Therefore, we do not consi necessary to exceed a dose of 2,000—rads in such cases. Intraperitoneal a trapleural application of radioactiv loidal substances, as gold or yttriun proved to be of value in such cases.

In cases of obvious ovarian can seems, from a clinical, prognostic and apeutic point of view, important to the cases with regard to the histopath structures most frequently seen. The ence center of the WHO recommends ing the tumors in serous, mucinous, metrioid, mesonephric and concomita mors. The serous carcinoma is the common and also the most malignal the great majority of patients with : carcinoma, extrapelvic metastases are at laparotomy. The endometrioid an sonephric carcinomas amount to abo per cent of the ovarian carcinomas. are frequently bilateral and give r metastases in the pelvis at an early Mucinous tumors are less frequent the endometrioid carcinomas. They giv to metastases comparatively late. N tases from mucinous carcinoma are times rather few.

At the Radiumhemmet, 366 cas serous, 63 cases of mucinous, 201 ca endometrioid and mesonephric, an cases of concomitant and unclassifie vious carcinomas have been examined a view to treatment, in the years 19 1962 inclusive. Irradiation has beer ployed in combination with surgery. rule, the uterus was spared in ord apply radium to the uterine cavity a this way apply a rather heavy dose or diation to the pelvis, where extension recurrences arising from ovarian c are most frequently seen, mainly in posterior and the anterior cul de sac.

In the years in question external in tion at the Radiumhemmet could on given with orthovoltage therapy. Th of the fields was dependent on the cl findings. The dose applied varied from

to case, according to the general condition of the patient, the age of the patient, the extension of the disease and many other factors. A maximum dose of 2,400 rads was given in 1 series to the lower abdomen. The corresponding dose to the upper abdomen was 2,000 rads from external irradiation. This radiation was only given in cases with extensive metastases. Provided the disease responded satisfactorily to the irradiation and the patient's general condition improved, the irradiation was later repeated, sometimes with the same dose. sometimes with a smaller dose. Consequently, a split technique has been used. Lenz has, in a brilliant way, studied several hundred cases of ovarian cancer treated at the Radiumhemmet. He has concluded that endometrioid and mesonephric sarcinomas have a better prognosis than serous carcinomas. He believes that the former groups of tumors respond better to irradiation than the serous carcinomas. Lenz's important studies have been of great value for the further work carried out at Radiumhemmet.

In the years 1958-1962, I have investigated in detail all cases of ovarian cancer treated during this period. Seven hundred and sixty-seven cases of obvious ovarian carcinoma have been examined with the view of therapy. As a rule, surgery has been the initial therapy. In all cases irradiation has been administered postoperatively. Preoperative irradiation has sometimes been given in patients with fixed ovarian tumors. Unfortunately, only conventional roentgen-ray therapy was available at the Radiumhemmet during these 5 years. In order to estimate the value of radiation, I give the figures for cases with metastases or/and cases with incompletely removed or inoperable ovarian cancer. In 97 cases of obvious serous cancer, the disease was limited to the pelvis, but it could not be removed completely at surgery. The 5 year survival rate among these 97 cases amounts to 23 per cent. Similar observations were made in 93 cases of endometrioid and mesonephric carcinomas. The 5 year

survival rate in these 93 cases amounts to 60 per cent. In 205 cases of serous carcinoma the cancer had given rise to extrapelvic metastases. The survival rate in these 205 cases amounts to 4 per cent. In 56 cases of endometrioid and mesonephric carcinoma extensive metastases were diagnosed. The survival rate in these 56 cases amounts to 15 per cent. These results support the observations by Lenz and speak in favor of the fact that endometrioid and mesonephric carcinomas respond better to irradiation than serous carcinoma. Mucinous carcinomas are no doubt more benign: they are radioresistant, and therefore extensive surgery is indicated for their treatment.

The observations described serve as proof that therapy in ovarian carcinoma should be individualized.

In more recent years the treatment of ovarian cancer at the Radiumhemmet has been applied along these established lines and will be continued as follows.

In a great majority of ovarian carcinomas surgery will be the initial treatment. The surgeon will outline in detail the extent of the disease and, if possible, he will ask the pathologist to perform frozen sections of biopsies taken during the course of laparotomy. Postoperative irradiation will be applied to all cases of obvious ovarian cancer provided the disease is completely removed or the extension of the growth and its metastases is restricted to the pelvis or/and lower abdomen. An exception to this rule is mucinous carcinoma. A dose of 4,500 to 5,000 rads will be given to the lower abdomen and the pelvis through one anterior and one posterior field, covering the whole area. The irradiation is done with a kilocurie cobalt 60 unit. The focus skin distance amounts to 80 cm. In addition to this radiation, radium is sometimes inserted into the uterus, if hysterectomy has not been performed. Such a treatment has proved to be of value, especially in cases in which the tumor is fixed in the true pelvis. Although it is not possible to present a series of cases treated for at least 5 years,

it is evident that irradiation is of considerable value, especially in cases of endometrioid and mesonephric carcinomas.

In cases of ovarian carcinoma with metastases to the upper abdomen, the treatment will depend on the extension of the disease and on the condition of the patient. As a rule, one should not exceed a dose of 2,000 to 2,500 rads to the upper abdomen. Two patients who received a dose of 3,500 rads to the upper abdomen through one anterior and one posterior field covering all tissue including the kidneys, have developed radiation nephritis. In several cases we have given radiation to the upper abdomen and have protected the kidneys with lead shields. The results have been poor. The same holds valid for cases treated with the so-called strip technique recommended at the M. D. Anderson Hospital. As a matter of fact, this strip technique seems to us difficult to apply, especially as the configuration of the abdomen changes from day to day.

Experimentally, it has been shown that the kidneys will support a dose higher than 2,500 rads, if about one-third of the organ is not included in the radiation field. An irradiation of the upper abdomen, therefore, requires very careful planning. We have tried to increase the dose to the upper abdomen to a value of 3,500 rads. The irradiation was given through one anterior and two lateral fields with the help of wedge filters. In 1964 and 1965, 18 patients with serous and 5 patients with endometrioid ovarian cancer were treated with this technique, in addition to the irradiation given to the lower abdomen and pelvis. In all the 23 cases very extensive metastases were found in the upper abdomen. Six out of the 18 patients with serous carcinoma and 3 of the 5 patients with endometrioid carcinoma are living and are in good health at 5 years following initial therapy. Two of the 9 patients are suffering from intestinal complications: one has a colostomy, the other developed severe reaction of the small intestine, necessitating resection of the lower ileum. A careful investigation of the kidney

function has been carried out in 4 of the 9 living patients. No sign of kidney damage has been diagnosed.

There is no doubt that extensive irradiation of the whole abdomen carries with it a risk of injury to the small bowel, to the colon and to the urinary tract. Several of the patients treated with radiation to the lower abdomen and the pelvis are suffering from intestinal cramps and diarrhea, but many patients have practically no symptoms at all, nor any discomfort.

Chemotherapy has proved to be of great value, especially in cases of ovarian cancer of the serous type. We have not been satisfied with the application of chlorambucil. For many years we used tioThepa intravenously. In the last 4 years L-phenylalanine mustard (alkeran) has been the drug mostly employed in ovarian carcinoma with metastases above the umbilicus. The alkeran is administered intravenously in 500 cc. dextran with a dose of 1-1.5 mg. alkeran per kg. body weight. We have not lost any patients as a sequel of the alkeran treatment. Based on our experience, it is important to give the drug in such doses that very marked leukopenia and thrombocytopenia develop, since there is a correlation between the degree of toxicity and the effect on the cancer. The administration of alkeran is repeated many times depending on the reaction of the blood, the general condition of the patient, and the local findings in the tumor.

Chemotherapy can be combined with irradiation. It is difficult to decide how this combined treatment should be administered. In collaboration with hematologists and cytologists we have carried out studies, for instance, on the bone marrow. We have reached the conclusion that a combined treatment should start with irradiation. After a dose of about 2,000 rads to the pelvis there is an increased number of megakaryocytes in the bone marrow of the sternum. We feel that this is the time for the application of chemotherapy in addition to the radiation, provided that chemotherapy is desirable.

In 1968, Munnell concluded that a significant improvement in 5 year survival is due partly to more aggressive and more extensive surgery. Many gynecologists and surgeons share his opinion. Many gynecologists recommend the performance of extensive surgery also in ovarian cancer fixed to surrounding tissues by firm adhesions. Munnell's investigation of the cases treated at the Columbia University is of great interest, and I congratulate him on his study. However, I do not think that I can agree with his statement. Unfortunately, he has not subdivided the cases with regard to the various types of ovarian cancer. Therefore, the improved survival observed in his cases may be due to the fact that different types of tumors were treated in the periods of

It has been our experience that extensive surgery in cases of ovarian cancer will lead to poor results. The effort to dissect such a carcinoma tends to disseminate cancer cells. An exception from this rule is mucinous carcinoma. In the area of Stockholm, 104 patients suffering from ovarian cancer fixed to the surrounding organs have been operated upon by well trained gynecologists. The surgeon tried to remove as much as possible of the tumor, although it was fixed to the pelvic wall, the sigmoid, the

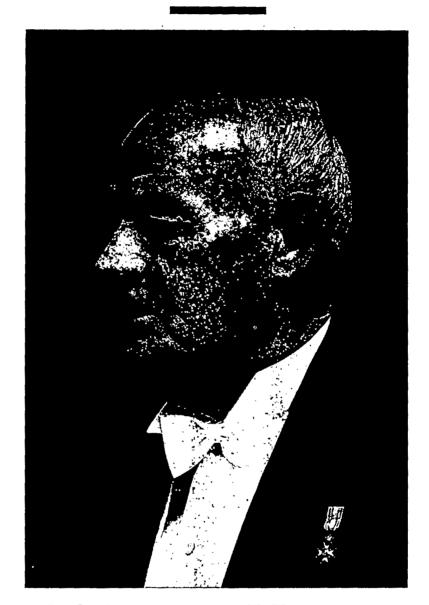
urinary bladder, or other tissues. All these patients received postoperative irradiation. None of the patients survived 21 months and the great majority of them died within 6 months following operation. In most of these cases the cancer was of serous type. The results are not better than the results observed in completely inoperable cases of obvious ovarian cancer. Therefore, we have recommended restriction of surgical intervention to an exploratory laparotomy. Irradiation has been applied with a dose of 3,000 to 4,000 rads in 4 to 7 weeks. The second look operation has been carried out 10 to 15 days following completion of radiotherapy. We have been astonished to find that the dissection of the growth was much easier to perform. Twenty out of 116 patients with obvious carcinoma fixed to the surrounding organs have been treated with this technique, and have survived for more than 3 years. The results are by no means satisfactory, but we believe that preoperative radiotherapy should be tried in selected cases of ovarian carcinoma.

This brief survey represents the present situation concerning the treatment of ovarian cancer in Sweden.

H.-L. KOTTMEIER, M.D.

Radiumhemmet Stockholm, Sweden





PROFESSOR ROBERT THORAEUS 1895–1970

PROFESSOR ROBERT THORAEUS, born on October 6, 1895, died on September 11, 1970, in Stockholm. He was well known in the world of radiology—not only because of his invention of the composed x-ray filter which carries his name—but also because of his many important contributions to radiation dosimetry.

Robert Thoraeus began working with

Rolf Sievert in the physics laboratory of Radiumhemmet (later called the Institute of Radiophysics) in 1927 and he was faithful to this laboratory throughout his life.

Investigations of qualitative and quantitative aspects of radiation beams became his major tasks and already in 1928, at the Second International Congress of Radiology, he presented his composite x-ray filter

—a considerable improvement in x-ray deep therapy. In 1932 he had successfully completed the design of a free-air ionization chamber which became for decades the basis for radiation dosimetry, not only in Sweden, but also in the other Scandinavian countries.

Robert Thoraeus organized the national ambulatory supervision program for x-ray therapy in Sweden and was the head of this section of the Institute of Radiophysics until 1958. Due to his technical skill and deep knowledge in the field of radiation physics he was able to found a solid basis for radiotherapy in Sweden. His genuine competence was also utilized in many international intercomparisons of dosimetry standards and he was for many years an active member of Committee II of the ICRU.

In 1958 Robert Thoraeus was appointed head of a new department for clinical radiation physics and became thereby responsible for the plans for expansion of the radiotherapy facilities at the Radiumhemmet including additional Co<sup>60</sup>-units, accelerators and auxiliary equipment for more accurate radiotherapy. After his retirement in 1965 he showed an unimpaired interest in radiation dosimetry and as Emeritus he continued his scientific work until a few weeks before his death.

Robert Thoraeus generously shared his genuine knowledge with his collaborators and many visitors. This gave him numerous true friends all over the world. They all recall the pleasure they had in experiencing his optimistic, openhearted and helpful working attitude and his strong personal interest in his friends.

RUNE WALSTAM

Professor of radiation physics Radiofysiska institutionen Karolinska sjukhuset 10401 Stockholm 60, Sweden



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# INTERNATIONAL REGIONAL CONGRESSES OF RADIOLOGY, 1971

AS INDICATED in the November 1970 issue (p. 648) of the JOURNAL, "Although the International Society of Radiology has not been concerned directly with the promotion of zonal activities, two large regional groups conduct regional congresses at intervals about midway between the International Congresses." These are the Inter-American Congress of Radiology, which will hold its Tenth Congress, May 16-22, 1971 in San Juan, Puerto Rico, and the European Association of Radiology which will hold its Second Congress, June 14-18, 1971 in Amsterdam, The Netherlands.

At the conclusion of the Twelfth International Congress of Radiology (Tokyo, 1969), through the initiative of Professor Kempo Tsukamoto, President of the International Society of Radiology, a third regional group was formed, the *Asian and Oceanian Society of Radiology*, which will hold its First Congress, November 22–26, 1971 in Melbourne, Australia.

#### TENTH INTER-AMERICAN CONGRESS OF RADIOLOGY

A preliminary announcement of the Tenth Inter-American Congress of Radiology, which will be held at the San Jeronimo-Hilton Hotel, in San Juan, Puerto Rico, May 16–22, 1971, was made in the May 1970 issue (p. 202) of this JOURNAL.

President Victor A. Marcial now extends a cordial invitation to all radiologists, allied scientists and friends to attend this meeting.

The meeting will afford a unique opportunity for radiologists from countries in this Hemisphere to exchange scientific data, to make new acquaintances and visit with old friends, and to enjoy the natural beauty and tourist facilities of the Island.

Puerto Rico, because of its location, language and culture, is the meeting center of the Americas. Its beaches, mountains,

pleasant tropical climate, Latin hospitality and great scientific and economic progress offer the visitors agreeable experiences.

A very outstanding program has been arranged with a distinguished Faculty presenting varied subjects in Radiodiagnosis and Radiotherapy. There will be Panels, Symposia, Conferences, Courses and Free Presentations.

The official Day-by-Day arrangements include: Saturday, May 15, arrival in San Juan; Sunday, May 16, the races at El Comandante, followed in the evening by a Welcome Reception; Monday and Tuesday, May 17 and 18, Scientific Sessions; Wednesday, May 19, Free, Sightseeing of old and new San Juan; Thursday and Friday, May 20 and 21, Scientific Sessions; Saturday, May 22, Proffered papers, Closing Ceremony.

After the meeting there will be 2 excursions: Extension A, St. Thomas, Virgin Islands, 4 days; and Extension B, the Exotic West Indies (Antigua, Barbados, Trinidad), 9 days.

The official travel arrangements to the Congress are sponsored by The American College of Radiology and made by Mr. Lee J. Kirkland of the Group Travel Services, Inc., 3537 Broadway, Kansas City, Missouri 64111.

The Congress is held under the auspices of the Inter-American College of Radiology. Officers of the College are: President, Dr. Juan A. del Regato, Penrose Cancer Hospital, 2215 North Cascade Avenue, Colorado Springs, Colorado 80907; Secretary, Dr. Fernando G. Bloedorn, Boston, Massachusetts; and Treasurer, Dr. Mario Vuksanovic, Miami, Florida. The Council of the College will meet during the Congress. The United States is represented in the Council by Dr. Manuel Viamonte, Jr., University of Miami School of Medicine, Miami, Florida.

The Program Committee is chaired by

Dr. Jimenez and the Vice-Chairman is Dr. Jesus. The radiodiagnostic portion of the program is headed by E. Torres Reyes; the radiotherapy section by Jose M. Tome; the nuclear medicine section by Aldo Lanaro; and the radiobiology and radiological physics sections by Jose N. Correa.

There will be scientific, technical and art exhibits.

Full information can be obtained by writing Dr. H. Pagan Saez, Secretary, Tenth Inter-American Congress of Radiology, Puerto Rico Nuclear Center, San Juan, Puerto Rico 235.

Arrangements are being made through Mr. Lee J. Kirkland for group travel of members of the American College of Radiology. The headquarters hotel for the ACR members will be the beachfront Puerto Rico Sheraton.

#### SECOND CONGRESS OF THE EUROPEAN ASSOCIATION OF RADIOLOGY

The Second Congress of the European Association of Radiology will be held at the International Congress Centre RAI, Amsterdam, Holland, June 14–18, 1971.

Holland is renowned for its windmills, its unusual hydraulic engineering, its beautiful scenery and for its wide variety of cultural aspects, national customs and communities. It is also a fascinating mixture of rural countryside, and large bustling populated areas with many industries and harbors.

Dr. J. R. von Roonen, President of the Congress, in issuing on behalf of the Organizing Committee a 56 page booklet of the "Provisional Programme," extends a most cordial invitation to attend. To quote from President von Roonen's invitation: "It is a long time since an international congress of radiology was organized in the Netherlands; such a long time, that you may be wondering whether we have lost the ability to organize such an event. Our answer to this, undoubtedly, would be 'we will do our best' to use the boyscouts' motto. And further we would add, dear

participant, come and convince yourself of our good intentions and our efforts to please you, and those accompanying you, both scientifically and socially."

The range of subjects, which will be covered at the meetings, includes: (1) Radiodiagnosis: A. Subjects for symposia: computers in diagnostic radiology; radiologic investigation of the liver; angiography of the regio retroperitonealis. B. Subjects for scientific sessions: Roentgen examination in organ transplantations; densitometry, cinemetry and videometry; early diagnosis of malignant diseases; pathological anatomy and roentgen diagnosis; roentgenology of the joints; radiological diagnosis of the orbita and the orbital contents: prenatal diagnosis; congenital malformations of the urinary tract; roentgenological investigations in the analysis of sterility; clinical physiological studies by x rays; roentgenologic examinations in centers of traumatology. (2) Radiotherapy and Physics: practical dosimetric problems in radiotherapy; techniques of planning and irradiation. (3) Radiotherapy and applied Radiobiology. (4) Radiotherapy: controlled clinical trials; tumors of the nasal sinuses; 'prophylactic' irradiation; combination of surgery and radiotherapy; indications for electron or neutron therapy; radiotherapy of relatively radioresistant tumors; failures and complications in radiotherapy. (5) Nuclear Medicine: dose calculation; dynamic studies; radioisotope scintigraphy; radiopharmaceuticals; radioisotope angiography. (6) Physics. (7) Technique. (8) Radiobiology. (9) Teaching; and (10) Professional Organization.

In presenting such an elaborate program, certain innovations will be made. For example, speakers of the age group of preferably 30-50 years will be selected, as they form a group of radiologists of whom, in general, it may be said that their scientific activities are at their optimum. Furthermore, much time will be reserved for review sessions and instruction courses. The former are intended for general orientation on the developments in a certain field; the

latter more for instruction in a specific research method or in special diseases, which, because of their rarity, make it difficult to obtain experience (for example bone tumors).

The proceedings, with the full text of all invited papers which have been handed over during the Congress, will be published within 8 months of the Congress.

The official languages of the Congress are English, French and German. Simultaneous interpretation from and into these languages will be provided in three halls.

On the occasion of the Congress a scientific exhibition will be arranged in the Congress building. A technical exhibition will be arranged in the 'Zuidhal' and 'Westhal' of the Congress building. There will also be an exhibition of books and periodicals, pertaining to the fields of Radiology and allied Sciences.

The Social Events are most attractive. Unless stated otherwise, excursions will be made by coach which will depart from and return to International Congress Centre RAI.

The Day-by-Day arrangements are as follows: Monday, June 14: Opening session for members and accompanying persons and an informal get-together: Tuesday, June 15: Sight-seeing tour of Amsterdam, for accompanying persons, Film evening for members and accompanying persons, special films, giving an impression of the Netherlands and its culture, will be shown; Wednesday, June 16: A choice of seven

excursions for accompanying persons, to 1. Aalsmeer and Muiderslot Castle, 2. The reclaimed land of the former Zuiderzee, 3. Holland-Waterland, 4. Hoorn and Enkhuizen: old towns on the former Zuiderzee, 5. Dordrecht and the Kinderdijk Windmills, 6. Katwijk and Noordwijk: walk on the beach and 7. Noordwijkerhout and Noodwijk: walk through the dunes and in the evening for members and accompanying persons, a special concert by the 'Concertgebouw' Orchestra under the baton of Bernard Haitink, followed by a Reception in the 'Rijksmuseum'; Thursday, June 17: A choice of 9 excursions for members and accompanying persons: 1. The Hague; 2. Rotterdam; 3. Gouda; 4. Haarlem; 5. Leiden; 6. Delft; 7. Vecht and Haarzuylen; 8. Show of old costumes in 'Duivenvoorde' Castle; and 9. Fashion Show in the Hague; Friday, June 18: Dutch Soirée for members and accompanying persons. Instead of the customary banquet, Dutch Soirée has been planned at the International Congress Centre RAI. The host for this evening will Agfa-Gevaert, Antwerp-Leverkusen, who will provide special Dutch dishes and drinks, together with cheerful and varied entertainment.

The Secretariat before and after the Congress is c/o Holland Organizing Centre, 16 Lange Voorhout, The Hague, the Netherlands. The Secretariat during the Congress is International Congress Centre RAI, Europaplein, Amsterdam, the Netherlands.



#### **NEWS ITEMS**

### NEW OFFICERS OF THE RADIOLOGICAL SOCIETY OF NORTH AMERICA

At the Fifty-sixth Annual Meeting of the Radiological Society of North America held November 29-December 4, 1970, at the Palmer House in Chicago, Illinois, the following officers were elected: President-Reynold F. Brown, M.D., San Francisco, California: President-Elect-Herbert Stauffer, M.D.,\* Philadelphia, Pennsylvania; First Vice-President-E. Richard King, M.D., Richmond, Virginia; Second Vice-President-Sidney W. Nelson, M.D., Columbus, Ohio; Third Vice-President-Lucy F. Squire, M.D., New York, New York; Secretary-Maurice D. Frazer, M.D., Lincoln, Nebraska; Treasurer-Harold O. Wyckoff, Ph.D., Rockville, Maryland; and Historian-Howard P. Doub, M.D., Detroit, Michigan.

The Chairman of the Board of Directors is David S. Carroll, M.D., Memphis, Tennessee.

The Gold Medal of the Society was awarded to Cesare Gianturco, M.D., Urbana, Illinois.

The Fifty-seventh Annual Meeting of the Society will be held at the Palmer House in Chicago, Illinois, November 28— December 3, 1971.

### EIGHTEENTH ANNUAL AFIP COURSE IN ORAL PATHOLOGY

This course, which will be held March 1-5, 1971, provides dentists, physicians and trainees in oral and general pathology with a fundamental knowledge of various aspects of oral disease, and brings them abreast of recent developments in this field.

It is presented by specialists in oral and general pathology, oral surgery, periodontics, dental research and cancer investigation.

Developmental disturbances of the head, neck and oral region, inflammatory diseases

\* Deceased, December 18, 1970.

of the oral mucosa and jaws, the oral manifestation of certain systemic diseases and neoplasms of the oral cavity and related structures are discussed in detail and their clinical, roentgenographic and microscopic characteristics illustrated.

Lectures are correlated with case presentations and microscopic slide seminars and will be held at evening sessions.

The course is open to both civilian and military dentists and physicians. Early application is advised.

To apply, contact The Director, Armed Forces Institute of Pathology, ATTN: MEDEM-DE, Washington, D.C. 20305.

#### NEONATAL RADIOLOGY SEMINAR

The University of Wisconsin Medical Center in conjunction with the St. Mary's Hospital Medical Center is pleased to announce the Second Annual Neonatal Radiology Seminar which will be held April 15–17, 1971, at The Wisconsin Center, Madison, Wisconsin.

The seminar is a comprehensive course covering all aspects of radiologic diagnosis of diseases of the newborn.

The Guest Faculty includes: David H. Baker, M.D.; N. Thorne Griscom, M.D.; John L. Gwinn, M.D.; Victor G. Mikity, M.D.; and Leonard E. Swischuk, M.D.

The Program Chairman is Richard L. Wesenberg, M.D., Pediatric Radiologist, St. Mary's Hospital Medical Center, Madison, Wisconsin.

Early reservations are advised as registration is limited.

For further information please write to: Coordinator of Postgraduate Medical Education, The Wisconsin Center, 702 Langdon Street, Madison, Wisconsin 53706.

### CORNELL UNIVERSITY MEDICAL COLLEGE

Two Postgraduate Courses will be given under the sponsorship of the Department of Radiology, Cornell University Medical College, in April 1971.

1. Postgraduate Course in "Radiology of the Abdomen," April 22, 23, 24, 1971, consisting of the following topics: Inflammatory Disease of the Abdomen; Vector Concept in Localization of Abdominal Masses; Pathology of Abdominal Masses; Renal, Adrenal and Other Extraperitoneal Tumors; and Abdominal Trauma.

The Guest Faculty includes: Murray G. Baron, M.D., Morton A. Bosniak, M.D., Arthur R. Clemett, M.D., Richard M. Friedenberg, M.D., Alexander Gottschalk, M.D., Peter G. Herman, M.D., James J. McCort, M.D., and Wilhelm Z. Stern, M.D., in addition to the Local Faculty.

2. Postgraduate Course in "Bone and Joint Radiology," April 26, 27, 28, 1971, with the following subjects: Basic Anatomy and Physiology of Bone; Osteoporosis, Osteomalacia; Hyperparathyroidism 1°, 2°, 3°; and other miscellaneous subjects.

The Guest Faculty of this course includes: Harold G. Jacobson, M.D., William Martel, M.D., John E. Moseley, M.D., Alex Norman, M.D., and Elias Theros, M.D., supplementing a large Local Faculty.

For further information please contact: John A. Evans, M.D., Department of Radiology, Cornell University Medical College, 1300 York Avenue, New York, New York 10021.

### AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE

The Second AAPM Summer School is to be held at Trinity University, San Antonio, Texas, July 11-17, 1971, immediately following the AAPM Annual General Meeting in Houston, Texas.

The School is intended to cover in depth various physical aspects of *Diagnostic Radiology*. Enrollment is limited.

Further information can be obtained from Dr. N. Suntharalingam, Stein Research Center, Department of Radiology, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania 19107.

#### NATIONAL ACADEMY OF SCIENCES: NATIONAL RESEARCH COUNCIL

The National Academy of Sciences-National Research Council invites submission of current data on somatic, genetic, and environmental effects of low-level ionizing radiation, including effects on human growth and development. This material is requested whether or not it has been published. Work in progress which is yet to be reported is of particular interest. The request is made in order to assist an advisory committee of the National Research Council in its deliberations concerning ionizing radiation effects upon human populations.

Under the auspices of this committee, 4 subcommittees will evaluate the data obtained.

The 2 year study, begun in the Fall of 1970, is being directed by Cyril L. Comar, Professor and Head of the Department of Physical Biology, New York State Veterinary College, Cornell University. The 4 subcommittees and their chairmen, all members of the advisory committee, are: Somatic Effects, Arthur C. Upton, Dean, School of Basic Health Sciences, State University of New York at Stony Brook; Genetic Effects, James F. Crow, Professor and Chairman, Department of Medical Genetics, University of Wisconsin, Madison; Environmental Effects, Dr. Comar; and Effects on Growth and Development, Samuel P. Hicks, Professor of Pathology, University of Michigan Medical Center.

The study is being supported by the U.S. Department of Health, Education and Welfare.

Please send the material to the Division of Medical Sciences, Attention: Dr. A. W. Hilberg, National Academy of Sciences, 2101 Constitution Avenue, Washington, D.C. 20418.

## THE FACULTY OF RADIOLOGISTS Regulations for the Twining Medal

A prize of £50 will be awarded every second year to a Fellow of the Faculty of

Radiologists. It will be awarded alternately to a diagnostic radiologist and to a radiotherapist. At the time of submitting the entry, the Fellow must be of less than 6 years' standing. He should present a paper or papers describing the work carried out by him.

The conditions of the Award are: (1) the paper or papers must be the original work of the applicant; (2) the work must have been done at some time within the 6 years preceding the date of the application;

and (3) the material submitted may include published work or an M.D. or Ph.D. thesis. If a joint paper is submitted the applicant must state clearly the part of the work carried out by himself.

In 1971 applications from Fellows who are radiotherapists will be considered, and should be submitted to the Warden of the Fellowship of the Faculty of Radiologists, at the Royal College of Surgeons, Lincoln's Inn Fields, London, WC2A 3PN by September 30, 1971.



## **BOOK REVIEW**

A Text-Book of X-Ray Diagnosis. Volume V: The Pelvis and the Abdomen. By British authors in six volumes. Fourth edition. Edited by S. Cochrane Shanks, C.B.E., M.D., F.R.C.P., F.F.R., Consulting Radiologist, University College Hospital, London; and Peter Kerley, C.V.O., C.B.E., M.D., F.R.C.P., F.F.R., Consulting Radiologist, Westminster Hospital and the National Heart Hospital, London, England. Cloth. Pp. 524, with 423 figures. Price, \$22.00. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. 19105, 1970.

This reviewer was brought up during his early training in radiology on previous editions of the British authors. The book, and the section on the alimentary tract, was one of the highlights of required reading. It was instructive, beautifully written and well illustrated.

The present volume has not changed as fast as the times have changed. The language is still beautiful, the prose reads well, but many of the illustrations have not changed. The interesting, somewhat patronizing and chatty style of writing does not contain enough up-to-date information; many of the illustrations are not of the quality expected in a modern text.

There is an insufficient coverage of important and new conditions, and overindulgence with other conditions, such as "cecal stasis," "colic constipation," "rectal constipation," etc.

Many of the authors' statements are overly dogmatic, particularly in the discussion of techniques for demonstration and study of hiatus hernias. Advocacy of the use of inflated Foley balloons inside colostomies does not agree with present day experience and practice in most of the Western world.

The authors' tendency to coin words like "raspberry thorn fissuring," "rose thorn type of fissuring" and "mamillation" in describing colonic ulceration is a refreshing example of "nuts and bolts" descriptive terminology in diagnostic radiology: they are not the most instructive. The treatment of "disaccharide" deficiency, where the authors are studying disaccharidase deficiency, also falls in this category.

The treatment of Zollinger-Ellison syndrome, or esophageal motility disorders, is not up-to-

date. Also, there is no mention of Fleischner's important work, and there is no section on the pancreas and arteriography.

Despite omission of these more recent contributions to the radiologic literature, the book is highly recommended.

## ALEXANDER R. MARGULIS, M.D.

## BOOKS RECEIVED

RADIOLOGIC CLINICS OF NORTH AMERICA. Symposium on Diagnosis of Tumors of the Head and Neck. Guest Editor, Gerald D. Dodd, M.D. December, 1970, Volume VIII, No. 3. Cloth. Pp. 211, with many illustrations. W. B. Saurders Company, West Washington Square, Philadelphia, Pa. 19105, 1970.

EINFÜHRUNG IN DIE RÖNTGENDIAGNOSTIK. By Umberto Cocchi, Peter Thurn, and Egon Bücheler. Cloth. Pp. 426, with 508 illustrations. Price, DM 59.-. Georg Thieme Verlag, Stuttgart. In U.S.A. and Canada, Intercontinental Medical Book Corporation, New York, N. Y. 10016, 1970.

HEART SIZE DETERMINATION BY PHOTOFLUOROG-RAPHY. By Kaarina Touru-Kaisila, Institute of Roentgen Diagnostics, Helsinki University Central Hospital, Finland. Paper. Pp. 96, with some figures. Price, Sw. Kr. 35:— Acta Radiologica, Supplementum 295. Acta Radiologica, Box 2052, Stockholm 2, Sweden, 1970.

OTOSCLEROSIS: A TOMOGRAPHIC-CLINICAL STUDY. By Hans Rovsing, Department of Diagnostic Radiology, Rigshospitalet, Copenhagen, Denmark. Paper. Pp. 143, with some figures. Price, Sw. Kr. 35:- Acta Radiologica, Supplementum 296. Acta Radiologica, Box 2052, Stockholm 2, Sweden, 1970.

POPULATION SCREENING FOR FEMALE BREAST TU-MOURS: A CLINICAL INVESTIGATION IN MALMÖ, 1966 AND 1967. By Per Langeland, Department of Radiotherapy, General Hospital, Malmö, Sweden. Paper. Pp. 72. Price, Sw. Kr. 35: Acta Radiologica, Supplementum 297. Acta Radiologica, Box 2052, Stockholm 2, Sweden, 1970.

EFFECT OF CYSTEINE ON CHROMOSOME ABERRATIONS INDUCED BY RADIATION OF HUMAN LYMPHOCYTES IN VITRO. By Johan Edgren, Folkhälsan Institute of Genetics, and the Radiotherapy Clinic of the University Central Hospital, Helsinki/Helsingfors, Finland. Paper. Pp. 76. Price, Sw. Kr. 30:-Acta Radiologica, Supplementum 298. Acta Radiologica, Box 2052, Stockholm 2, Sweden, 1970. Selective Angiography of the Left Gastric Artery. By Rune Sundgren, Roebtgendiagnostic

Department, University Hospital, Lund, Sweden. Paper. Pp. 100, with many illustrations. Price, Sw. Kr. 35:-. Acta Radiologica, Supplementum 299. Acta Radiologica, Box 2052, Stockholm 2, Sweden, 1970.

Scientific Publications: from Eastman Kodak Laboratories. Section I, 1969: Organic Chemistry, Polymer Chemistry, Biological Chemistry, Paper. Pp. 103. Section II, 1969: Analytical Chemistry, Physical Chemistry, Chemical Engineering. Paper. Pp. 131. Section III, 1969: Physics, Mathematics, Engineering. Paper. Pp. 119. Section IV, 1969: Photographic Science and Technology. Paper. Pp. 113. Published by Department of Information Services, Research Laboratories, Eastman Kodak Company, Rochester, N. Y. 14650, 1970.

BIOLOGIC RELATIVITY. By E. R. N. Grigg, M.D.

Cloth. Pp. 257, with many figures. Price, \$9.50. Amaranth Books, Box 50392, Chicago Ill., 60650, 1967.

PROGRESS AGAINST CANCER, 1970: a Report by the National Advisory Cancer Council. Paper. Pp. 98, with many figures. Price, \$1.75. Superintendent of Documents, U.S. Government Printing Office, Washington, D. C. 20402, 1970.

3RD INTERNATIONAL SYMPOSIUM ON ASTHMA AND CHRONIC BRONCHITIS IN CHILDREN AND THEIR PROGNOSIS INTO ADULT LIFE, Davos, Switzerland, Oct. 23–24, 1969. Edited by F. Suter, Davos, Switzerland. Meeting on Disodium Chromoglycate (Intal/Lomudal®), Davos, Switzerland, Oct. 25, 1969. Edited by R. E. C. Altounyan, Leicestershire, England. Paper. Pp. 371, with many figures. Supplementum to Volume 27, 1970, of Respiration. S. Karger, Basel, Switzerland, 1970.



## SOCIETY PROCEEDINGS

## MEETINGS OF RADIOLOGICAL SOCIETIES\*

## United States of America

American Roentgen Ray Society

Secretary, Dr. Ted F. Leigh, Emory University Clinic, Atlanta, Ga. 30322. Annual meeting: Sheraton Hotel, Boston, Mass., September 28-October 1, 1971.

AMERICAN RADIUM SOCIETY

Secretary, Dr. Jerome M. Vaeth, Saroni Tumor Institute, 1600 Divisadero St., San Francisco, Calif. 94115. Annual meeting: Mexico City, Mexico, March 15-18, 1971.

RADIOLOGICAL SOCIETY OF NORTH AMERICA Secretary-Treasurer, Dr. Maurice Doyle Frazer, 1744 South Fifty-eighth St., Lincoln, Neb. Annual meeting: Palmer House, Chicago, Ill., November 28-December 3,

AMERICAN COLLEGE OF RADIOLOGY Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill. Annual meeting: St. Louis, Mo., Chase-Park Hotel, March 30-April 3, 1971.

Section on Radiology, American Medical Association Secretary, Dr. Ted F. Leigh, Emory University Clinic, Atlanta, Ga., 30322. Annual meeting: Atlantic City,

N. J., June 20-24, 1971.

AMERICAN BOARD OF RADIOLOGY

Secretary, Dr. C. Allen Good. Correspondence should be directed to Kahler East, Rochester, Minn. 55901.

Oral examinations will be held in the following cities

during the next 2 years: Bal Harbour, Fla., June 7-11, 1971, Americana Hotel; Dallas, Tex., Dec. 6-10, 1971, Statler-Hilton Hotel; Washington, D.C., June 5-9, 1972, Washington-Hilton Hotel; and Atlanta, Ga., Dec. 4-8, 1972, Sheraton-Biltmore Hotel.
Written examinations are scheduled in June of each

year in 13 large centers, and applications must be re-ceived in the Board Office before Sept. 30 of the year preceding the one in which the candidate wishes to be examined. The written examinations this year will be held on June 19, 1971.

Deadline for filing applications for any examination

in 1972 is September 30, 1971.

American Association of Physicists in Medicine Secretary, Leonard Stanton, Hahnemann Medical College 230 N. Broad St., Philadelphia, Pa. 19102. Annual meeting to be announced.

AMERICAN SOCIETY OF THERAPEUTIC RADIOLOGISTS Secretary, Dr. Carl R. Bogardus, Jr., University of Okla-homa Medical Center, Oklahoma City, Oklahoma 73104

AMERICAN INSTITUTE OF ULTRASOUND IN MEDICINE
Secretary, F. J. Fry, M.Sc., Bioacoustics Lab., University
of Illinois, Urbana, Ill.

AMERICAN SOCIETY OF NEURORADIOLOGY

Secretary-Treasurer, Dr. Eugene V. Leslie, Edward J.

Meyer Memorial Hospital, 462 Grider St., Buffalo, N. Y.

THIRTEENTH INTERNATIONAL CONGRESS OF RADIOLOGY Meeting: Madrid, Spain, Oct. 13-19, 1973.

TENTH INTER-AMERICAN CONGRESS OF RADIOLOGY Counselor for the United States, Dr. Manuel Viamonte, Jr., University of Miami School of Medicine, Jackson Memorial Hospital, Miami Fla. 33136. President, Dr. Victor A. Marcial, Puerto Rico Nuclear

Center, Caparra Heights Station, San Juan, Puerto Rico ∞935.

Meeting: San Jeronimo-Hilton Hotel, San Juan, Puerto Rico, May 16-22, 1971.

Inter-American College of Radiology President, Dr. Juan A. del Regato, Penrose Cancer Hospital, 2215 North Cascade Ave., Colorado Springs, Colo.

80907.
Second Congress of the European Association of RADIOLOGY

President, Professor Dr. J. R. von Roanen, State University of Leiden, The Netherlands.

Voorhout, The Hague, The Netherlands. Congress Meeting: Amsterdam, The Netherlands, June 14-18,

FIRST ASIAN AND OCEANIAN CONGRESS OF RADIOLOGY Honorary Secretary, Dr. J. J. Martin, Box 805 F., G.P.O., Melbourne, 3001, Australia. Meeting: Melbourne, Australia, Nov. 22-26, 1971.

ALABAMA CHAPTER OF ACR Secretary, Dr. William V. Weldon, Medical Arts Building, Birmingham, Ala. 35205. Meets time and place of Alabama State Medical Association.

ALASKA RADIOLOGICAL SOCIETY

Secretary, Dr. Bruce C. Wright, Providence Hospital, Anchorage, Alaska. Meets third Wednesday each month. ARIZONA RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary, Dr. Wesley S. Fee, 2421 E. 6th St., Tucson, Ariz, 85719. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

ARKANSAS CHAPTER OF ACR

Secretary-Treasurer, Dr. Wilma C. Diner, Univ. of Arkansas Medical Center, Little Rock, Ark. 72201. Meeta twice annually, the Spring Meeting being in conjunction with and at the place of the State Medical Association.
Association of University Radiologists

Secretary-Treasurer, Dr. Elliott C. Lasser, University Hospital of San Diego County, San Dego, Calif. 92103. Annual Meeting: Durham, N. C., May 13-15, 1971, with the Duke University and University of North Carolina

Radiology Departments serving, as co-hosts. Atlanta Radiological Society Secretary, Dr. Richard S. Colvin, Emory University Clinic, Atlanta, Ga. 30322. Meets on four Thursday evenings during the academic year at a time announced in early September of each year, at the Academy of Medi-

cine, Atlanta, Ga., at 8:00 p.m. BAVARIAN-AMERICAN RADIOLOGIC SOCIETY

Advisor, Colonel Paul E. Sieber. Secretary, LTC Peter B. Riesz, USAH Bad Cannstatt, APO 29154, New York, N. Y. Meets quarterly.

BLOCKLEY RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. R. John Gould, 41 Lombardy Rd., Drexel Hill, Pa. 19026.

BLUEGRASS RADIOLOGICAL SOCIETY

Secretary-Treasurer, Joseph A. Sayeg, Ph.D., Radiation Physicist, University of Kentucky, Lexington, Ky. 40506. The Society meets once each month during the school year.

BRONX RADIOLOGICAL SOCIETY, NEW YORK STATE, CHAP-TER ACR

Secretary-Treasurer, Dr. David Bruce Hayt, 600 E. 233rd St., Bronx, N. Y. 10466. Meets 4 times a year.

BROOKLYN RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Kenneth B. Robinson, 301 E 75th St., Apt. 11-A, New York, N.Y. 10021. Meets first Thursday of each month, October through June.

BUFFALO RADIOLOGICAL SOCIETY Secretary, Dr. Glen M. Ebersole, 405 Spring St., Jamestown, N.Y. 14701. Meets second Monday evening each month, October to May inclusive, at University Club.

\* Secretaries of societies are requested to send timely information promptly to the Editor.

CALIFORNIA RADIOLOGICAL SOCIETY, CALIFORNIA CHAPTER

Secretary-Treasurer, Dr. John L. Gwinn, Childrens Hospital of Los Angeles, P.O. Box 54700, Los Angeles, Calif.

CATAWBA VALLEY RADIOLOGICAL SOCIETY

Secretary, Dr. Emmett R. White, P. O. Box 10, Rutherford College, N. C. 28671. Meets every Thursday, Dept. of Radiology, Valdese General Hosp., Valdese, N. C., at 12:30 P.M.

CENTRAL NEW YORK RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. David N. Cheris, Community
General Hospital of Greater Syracuse, Broad Road,
Syracuse, N. Y. 13215. Meets first Monday each month
October through May.

CENTRAL OHIO RADIOLOGICAL SOCIETY
Secretary, Dr. James V. Blazek, 2586 Lane Rd., Columbus, Ohio 43220. Meets second Thursday in October, November, January, and March 15, and May 19 at Fort Hayes Hotel, Columbus, Ohio.

CHICAGO ROENTGEN SOCIET

Secretary-Treasurer, Dr. William T. Moss, 250 E. Superior St., Chicago, Ill. 60611. Meets third Thursday of each month, October to April, except December, at the

Bismarck Hotel, Chicago, Ill. CLEVELAND RADIOLOGICAL SOCIETY

Shaker Blvd., Cleveland, Ohio 44104. Meetings at 7:00 P.M. on fourth Monday of October, November, January,

February, March and April.
Colorado Radiological Society, Chapter of ACR Secretary, Dr. Marvin L. Daves, Univ. of Colorado Medical Center, 4200 E. Ninth Ave., Denver, Colo. 80220. Meets third Friday of each month at Denver Athletic Club from September through May.

Connecticut Valley Radiologic Society Secretary, Dr. William W. Walthall, Jr., 130 Maple St., Springfield, Mass. Meets in April and October.

DALLAS-FORT WORTH RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. V. V. Kirby, 1722 Spring Lake Dr., Arlington, Tex. 76010. Meets the 3rd Monday of every month at 6:30 P.M., at the Cibola Inn, Arlington,

DELAWARE CHAPTER OF ACR

Secretary, Dr. James H. Taylor, Wilmington Medical Center, Wilmington, Del. 19899.

EAST BAY RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. S. Walter Kran, Doctors' Hospital of San Leandro, 13855 East 14th St., San Leandro, Calif. 94578. Meets first Thursday each month, Oct. through May, at University Club, Oakland, Calif.

EAST TENNESSEE RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Eberhard F. Besemann, Baroness Erlanger Hospital, Chattanooga, Tenn. 37403. Meets in January and September.

FLORIDA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Wm. F. Lindsey, 1215 Hodges Dr., Tallahassee, Fla. 32303. Meets twice annually, in the spring with the annual State Society Meeting and in the fall.

FLORIDA WEST COAST RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Allen L. Sheer, University Community Hospital, 13505 N. 31st St., Tampa, Fla. 33612. Meets in January, March, May, July, September and November.

GEORGIA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Walker Harris, The Medical Center, Columbus, Ga. 31902. Meets in spring and fall at Annual State Society Meeting.

Greater Cincinnati Radiological Society

Secretary-Treasurer, Dr. Owen L. Brown, 2421 Auburn Ave., Cincinnati, Ohio 45219.

GREATER LOUISVILLE RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. L. D. LeNerve, 315 E. Broadway, Louisville, Ky. 40202. Meets monthly.
Greater Miami Radiological Society

Secretary-Treasurer, Dr. John Kathe, North Shore Hospital, Miami, Fla. 33150. Meets monthly, third Wednes-

day at 8:00 P.M. at various member hospitals, Miami, Fla. GREATER ST. LOUIS SOCIETY OF RADIOLOGISTS

Secretary-Treasurer, Dr. Roland P. Ernst, 3720 Wash-

ington Ave., St. Louis, Mo. 63108.

Hawaii Radiological Society, Chapter of ACR

Secretary-Treasurer, Dr. Virgil R. Jobe, Jr., 888 South

King St., Honolulu, Hawaii 96813. Meets third Monday

of each month at 7:30 P.M.

HEALTH PHYSICS SOCIETY

Secretary. John H. Pingel, Argonne National Laboratory, 9700 S. Cass Ave., Argonne, Ill. 60439, Annual Meeting: Waldorf Astoria Hotel, New York City, July 11-15,

HOUSTON RADIOLOGICAL SOCIETY

Secretary, Dr. Kenneth M. Jensen, 1615 St. Joseph Prof. Bldg., Houston, Texas 77002. Meets fourth Monday of each month, except June, July, August and December, at 6:00 P.M., at 103 Jesse H. Jones Library Building, Texas Medical Center, Houston, Tex. 77025 IDAHO STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary, Dr. Hugh P. Smith, Jr., 130 E. Bannock, Boise, Id. 83702. Meets in the spring and fall.

ILLINOIS RADIOLOGICAL SOCIETY, INC., CHAPTER OF ACR Secretary, Dr. Jack L. Melamed, 1230 Sunset Rd. Winnetka, Ill. 60093. Meets in the spring and fall.

INDIANA ROBNIGEN SOCIETY, INC., CHAPTER OF ACR Secretary, Dr. Dale B. Parshall, Elkhart General Hospital, P.O. Box 1329, Elkhart, Ind. 46514.

IOWA RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary-Treasurer, Dr. John Huston Jr., 1948 First Ave. N.E., Cedar Rapids, Iowa 52402. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn

KANSAS RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Wm. R. Allen, 155 S. 18th St. Kansas City, Kan. 66102. Meets in spring with State Medical Society and in winter on call.

KENTUCKY CHAPTER OF ACR

Secretary-Treasurer, Dr. Joan R. Hale, 402 Heyburn Bldg. Louisville, Ky. 40202. Meets in April and September.

KINGS COUNTY RADIOLOGICAL SOCIETY

Secretary, Dr. Sidney Hendler, 1880 Ocean Ave., Brooklyn 30, N.Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

KNOXVILLE RADIOLOGICAL SOCIETY
Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

Long Island Radiological Society

Secretary, Dr. Harold L. Atkins, 1200 Stewart Ave.,
Garden City, N. Y. 11533. Meets monthly.

Los Angeles Radiological Society

Secretary, Dr. Harry T. Vanley, St. Mary's Long Beach Hospital, Long Beach, Calif. 90083. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Associa-tion Building, Los Angeles, Calif. Annual Midwinter Conference: Jan 30-31, 1971. LOUISIANA-TEXAS GULF COAST RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Edward A. Sheldon, 109 Doctors

Bldg., Beaumont, Tex. 77701

Maine Radiological Society, Chapter of ACR

Secretary-Treasurer, Dr. Richard W. Taylor, Radiology Department, St. Mary's General Hospital, Lewiston, Maine 04240. Meets in June, September, December and April. MARYLAND RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary, Dr. Nathan Stofberg, 4519 Hawksbury Rd.,

Pikesville, Md. 21208.

MASSACHUSETTS RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Norman L. Siadowsky, The Faulkner Hosp., 1153 Centre St., Jamaica Plain, Mass. 02130 MEMPHIS ROENTGEN SOCIETY

Secretary-Treasurer, Dr. Webster Riggs, Jr., The University of Tennessee College of Medicine, Department of

Radiology, Walter F. Chandler Bldg., 865 Jefferson Ave., Memphis, Tenn. 38103. Meets first Monday of each month at John Gaston Hospital.

MIAMI VALLEY RADIOLOGICAL SOCIETY

Secretary, Dr. Darwood B. Hance, Reid Memorial Hospital, Richmond, Ind. Meets third Thursday of fall, winter and spring months at 7:30 P.M. at Miami Valley

Hospital, Dayton, Ohio.
MICHIGAN RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. David P. Corbett, Harper Hospital, Detroit, Mich. 48201. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antie-

tam, at 6:30 P.M.

MID-HUDSON RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Herbert S. Berlin, Hopewell Junction, N. Y. Meets 7:00 P.M., first Wednesday of each month, September to May.

MILWAUKEE ROENTGEN RAY SOCIETY

Secretary-Treasurer, Dr. James E. Bell, 8700 W. Wisconsin Ave., Milwaukee, Wis. 53213. Meets monthly on fourth Monday, October through May, at University Club.

MINNESOTA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Warren L. Kump, 4243 Glenwood Ave., Minneapolis, Minn. 55422. Meets twice annually, fall and winter.

MISSISSIPPI STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary-Treasurer, Dr. Ottis G. Ball, 5356 Balmoral Drive, Jackson, Miss. 39211. Meets third Thursday of each month at the Heidelberg Hotel, Jackson, at 6:00 P.M.

MISSOURI RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Arthur A. Porporis, 100 N. Euclid Ave., St. Louis, Mo. 63108.

MONTANA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Jon A. Anderson, Doctor's Building, 1231 N. 29th Street, Billings, Mont. 59101.

NEBRASKA CHAPTER OF ACR Secretary-Treasurer, Dr. Gordon F. Johnson, 4239 Farnam, Omaha, Neb. 68131. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

NEVADA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Harris W. Knudson, 2020 W. Charleston Blvd., Las Vegas, Nev. 89102.

New England Roentgen Ray Society
Secretary, Dr. Stefan C. Schatzki, 1180 Beacon St.,
Brookline Mass. 02146. Meets third Friday of each month, October through April, excluding December, at The Longwood Towers, 20 Chapel Street, Brookline, Mass., at 4:30 P.M.

NEW HAMPSHIRE ROENTGEN RAY SOCIETY, CHAPTER OF

Secretary, George Farmlett, 33 Round Bay Rd., Keene, N. H. 03246. Meets four to six times yearly.

New Mexico Society of Radiologists Chapter of ACR Secretary, Dr. Donald A. Wolfel, Albuquerque, New Mexico. Four meetings annually, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

NEW YORK ROENTGEN SOCIETY Secretary-Treasurer, Dr. Samuel H. Madell, I. E. 82nd St., New York, N. Y. 10028. Meets monthly on third Monday at the New York Academy of Medicine at 4:30 P.M. Annual Spring Conference: Waldorf Astoria Hotel, New York, April 29-May 1, 1971. Further information may be obtained from Dr. Albert A. Dunn, Roosevelt Hosp., New York, N. Y. 10019.

NEW YORK STATE CHAPTER OF ACR

Secretary-Treasurer, Dr. John J. Magovern, 520 Frank-lin Ave., Garden City, N. Y. 11530.

NORTH CAROLINA CHAPTER OF ACR.

Secretary-Treasurer, Dr. James F. Martin, 300 S. Hawthorne Road, Winston-Salem, N. C. 27103.

NORTH DAKOTA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Marshall Landa, 1702 13th St., So., Fargo, N. D. 58102. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

NORTH FLORIDA RADIOLOGICAL SOCIETY

Secretary, Dr. John W. Morris, III., Department of Radiology, Halifax District Hospital, Daytona Beach, Fla. 32015. Meets quarterly in March, June, September and December.

NORTHEASTERN NEW YORK RADIOLOGICAL SOCIETY Secretary, Dr. Barbara Chick, Glens Falls Hospital, Glens Falls, N.Y. 12801. Meets in Albany area on third Wednesday of October, November, Narch, April, and

NORTHERN CALIFORNIA RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Kevin Ryan, Woodland Medical group, Woodland, Calif. 95695. Mee:s fourth Monday of Sept., Nov., Jan., March and May at Aldo's Restaurant in Sacramento.

NORTHWESTERN OHIO RADIOLOGICAL SOCIETY

Secretary, Dr. Vito J. Zupa, Mercy Hospital, Department of Radiology, Toledo, Ohio.
Ohio State Radiological Society, Chapter of ACR

Secretary, Dr. Joseph Hanson, 1544 Scuth Byrne Road, Toledo, Ohio 43614.
Orlahoma State Radiological Society, Chapter of

ACR

Secretary, Dr. Richard B. Price, 20. Medical Tower Bldg., Oklahoma City, Okla. 73112. Meets in January, May and October.

ORANGE COUNTY RADIOLOGICAL SOCIETY Secretary, Dr. Edward I. Miller, 301 Newport Blvd., Newport Beach, Calif. 92660. Meets on fourth Tuesday of the month, excluding June, July, August, and December, at the Orange County Medical Association Bldg.,

Orange, Calif.
OREGON STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Gerlad L. Warnock, 11699 N. E. Glisan St., Portland, Ore. 97220. Meets on second Wednesday of month, October through April, at the University Club, Portland, Ore.

Orleans Parish Radiological Society Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans, La. 70113. Meets second Tuesday of each month.

PACIFIC NORTHWEST RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Robert S. Miller, 13753 S.W. Farmington Rd.; Beaverton, Oregon 97005. Meets annually in Portland, Oregon, Seattle, Washington or Victoria or Vancouver, British Columbia, in early May.

PENNSYLVANIA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Theodore A. Tristan, Harrisburg Polyclinic Hosp., Harrisburg, Pa. 17105.

PHILADELPHIA ROENTGEN RAY SOCIETY

Secretary, Dr. C. Jules Rominger, Misericordia Hospital, 54th St. and Cedar Ave., Philadelphia, Pa. 19143. Meets first Thursday of each month at 5 P.k., from October to May in Thompson Hall, College of Physicians.

PITTSBURGH ROENTGEN SOCIETY Secretary, Dr. Stephen C. Bruno, Shadyside Hospital, 5230 Centre Ave., Pittsburgh, Pa. 15232. Meets second Wednesday of month, October through June, at Park Schenley Restaurant.

RADIATION RESEARCH SOCIETY Executive Secretary, Richard J. Burk, Jr., 4211 39th St.,

N.W., Washington, D. C. 20016. RADIOLOGICAL SOCIETY OF CONNECTICUT, INC., CHAPTER or ACR

Secretary-Treasurer, Dr. Carl W. Scheer, 335 Cook Ave., Meriden, Conn. 06450. Meeting: are held quarterly RADIOLOGICAL SOCIETY OF GREATER CINCINNATI

Secretary-Treasurer, Dr. Donald E. Gunderson, 3553 Bayard Dr., Cincinnati, Ohio 45208. Meets first Monday of each month at Cincinnati Academy of Medicine.

RADIOLOGICAL SOCIETY OF GREATER KANSAS CITY Secretary, Dr. Ken C. Davidson, Sr. Luke's Hospital of Kansas City, Kansas City, Mc. 84111. Meets 5 times a year on given dates.

RADIOLOGICAL SOCIETY OF KANSAS CITY

Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month

RADIOLOGICAL SOCIETY OF LOUISIANA, CHAPTER OF ACR Secretary, Dr. Ralph B. Bergerson, 154 Brockenbraugh Ct. Metairie, La. 70005. Meets semiannually during Louisiana State Medical Society meeting and 6 months

RADIOLOGICAL SOCIETY OF NEW JERSEY, CHAPTER OF ACR Secretary, Dr. Sidney Ketyer, St. Elizabeth Hosp., 225 Williamson St., Elizabeth, N. J. 07207. Meets in Atlantic City at time of State Medical Society meeting and in October or November in Newark, N. J.

RADIOLOGICAL SOCIETY OF RHODE ISLAND, CHAPTER OF

Secretary-Treasurer, Dr. John J. O'Brien, 292 Merry-

mount Dr., Warwick, R.I. 02888.

RADIOLOGICAL SOCIETY OF SOUTHERN CALIFORNIA Secretary-Treasurer, Dr. Gladden V. Elliott, 5565 Gross-mont Center Dr., Suite 1, La Mesa, Calif. 92041. Meets three times a year, usually October, February and May. RADIOLOGICAL SOCIETY OF THE STATE OF NEW YORK

Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester, N. Y. 14618.

REDWOOD EMPIRE RADIOLOGICAL SOCIETY Secretary, Dr. Lee F. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

RICHMOND COUNTY RADIOLOGICAL SOCIETY

Secretary, Dr. M. Pinson Neal, Jr., Medical College of Virginia, 1200 E. Broad St., Richmond, Va. 23219. Meets first Thursday of each month at various hospitals.

ROCHESTER ROENTGEN RAY SOCIETY, ROCHESTER, N. Y. Secretary, Dr. Kenneth E. Robinson, Rochester General Hospital, 1425 Portland Ave., Rochester, N. Y. 14621. Quarterly meetings on the call of the President, at the Rochester Academy of Medicine.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Lorenz R. Wurtzebach, 4200 E. Ninth Ave., Denver. Colo. 80220. Annual meeting: Brown Palace Hotel, Denver, Colo., Aug. 19–21, 1971.

SAN ANTONIO-CIVILIAN-MILITARY RADIOLOGICAL SOCIETY Secretary, Dr. Lee F. Rogers, Department of Radiotherapy, Bexar County Teaching Hospital, 4502 Medical Drive, San Antonio, Texas. Meets third Wednesday of each month at Fort Sam Houston Officers' Club at 6:30 P.M.

SAN DIEGO RADIOLOGICAL SOCIETY

President-Secretary, Dr. Q. H. Lehmann, 5565 Grossmont Center Dr. Suite 1, La Mesa, Calif. 92041. Meets first Wednesday of each month at the Town & Country Hotel.

SAN FRANCISCO RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Warren M. Russel, Franklin Hospital, Castro & Duboce, San Francisco, Calif. 94114. Meets quarterly at various hospitals (contact Secretary).

SANTA CLARA COUNTY RADIOLOGICAL SOCIETY

Secretary, Dr. Emory G. West, 285 S. Drive, Mt. View, Calif. 94040. Meets monthly at the Santa Clara County Medical Association Bldg., 700 Empey Way, San Jose, Calif.

SECTION ON RADIOLOGY, CALIFORNIA MEDICAL ASSOCIATION Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Medical Society of the Dis-trict of Columbia

Secretary-Treasurer, Dr. Louis Wener, Cafritz Memorial Hosp., 1310 Southern Ave., S.E., Washington, D. C. 20032. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

SECTION ON RADIOLOGY, SOUTHERN MEDICAL ASSOCIATION Secretary, Dr. Phillip W. Voltz, Jr., 120 Medical Professional Bidg., San Antonio, Tex. 78212.

SECTION ON RADIOLOGY, TEXAS MEDICAL ASSOCIATION Secretary, Dr. George F. Crawford, St. Elizabeth Hospital, Beaumont, Tex. Meets annually with the Texas Medical Association.

SHREVEPORT RADIOLOGICAL CLUB

Secretary, Dr. W. R. Harwell, 608 Travis St., Shreveport,

La. Meets monthly on third Wednesday at 7:30 P.M., September to May inclusive.

SOCIETY FOR PEDIATRIC RADIOLOGY

Secretary, Dr. John L. Gwinn, Children's Hospital, 4614 Sunset Blvd., Los Angeles 27, Calif. Annual meeting: Sheraton Hotel, Boston, Mass., September 26–27, 1971. SOCIETY OF NUCLEAR MEDICINE

Secretary, Dr. James J. Smith, 140 E. 54th St., New York, N. Y. Administrative Officer, Mrs. Margaret Glos, 211 E. 43rd St., New York, N. Y. 10017. Annual meeting: Los Angeles, Calif., June 26-July 2, 1971. South Bay Radiological Society

Secretary, Dr. Emerson C. Curtis, University Dr., Menlo Park, Calif. 94025. Meets second Wednesday of each month.

SOUTH CAROLINA RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

South Dakota Radiological Society, Chapter of ACR Secretary, Dr. Haskon O. Haugan, 716 Quincy St., Rapid City, S. D. 57701. Meets in spring with State Medical Society and in fall.

SOUTHERN CALIFORNIA RADIATION THERAPY SOCIETY Secretary-Treasurer, Dr. Aaron G. Fingerhut, 1000 W. Carson St., Torrance, Calif. 90502. Meets quarterly.

SOUTHERN RADIOLOGICAL CONFERENCE

Secretary-Treasurer, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 7544, Mobile, Ala. 36607. Annual meeting: Grand Hotel, Pointe Clear, Ala. Jan. 29-31, 1971. SOUTHWESTERN RADIOLOGICAL SOCIETY

Secretary, John M. McGuire, 904 Chelsea, El Paso, Tex. Meets last Monday of each month at 6:30 P.M. in

the Paso del Norte Hotel.

TENNESSEE RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Lawrence R. Nickell, Maury County Hospital, Columbia, Tenn. 38401. Meets annually at the time and place of the Tennessee State Medical Association and place of the Tennessee State Medical Association meeting.

TEXAS STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Herman C. Schested, 815 Medical Tower, Room 100, 1550 W. Rosedale St., Fort Worth, Tex. 76104. Annual meeting at the Flagship Hotel on Pier,

Galveston, Tex. THE FLEICHNER SOCIETY

Secretary-Treasurer, Eric N. C. Milne, M.B., Medical Sciences Bldg., University of Toronto, Ontario, Canada. Meets in Williamsburg, Va., March 1971, in conjunction with a course on "Modern Trends in Roentgenology of the Chest," sponsored by the Virginia Commonwealth University, Richmond, Va.

TRI-STATE RADIOLOGICAL SOCIETY

Secretary Descriptions of the Marchand In Markodiet Has

Secretary, Dr. John H. Marchand, Jr., Methodist Hospital, Henderson, Ky. Meets third Wednesday of Oct., Jan., March and May, 8:∞ P.M., Elks Club in Evansville, Ind.

University of Michigan Department of Roentgen-OLOGY STAFF MEETING

Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital, Ann Arbor, Mich.

Upper Peninsula Radiological Society Secretary, Dr. A. Gonty, Menominee, Mich. Meets

Utah State Radiological Society, Chapter of ACR Secretary-Treasurer, Dr. R. Newell Ford, St. Mark Hospital, 803 North 2nd West, Salt Lake City, Utah 84103. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.
VERMONT RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary, Dr. Edward A. Kupic, Mary Fletcher Hosp.,

Burlington, Vt. 05401.

VIRGINIA CHAPTER OF ACR
Secretary-Treasurer, Dr. James S. Redmond, Suite 7,
Medical Center, Lynchburg, Va. 24501.

Washington, D. C., Chapter of ACR Secretary-Treasurer, Dr. Joan Wohlgemuth, 5021 Sem-

inary Rd., Alexandria, Va. 22311. WASHINGTON STATE RADIOLOGICAL SOCIETY, CHAPTER OF

Secretary-Treasurer, Dr. Paul S. Paulson, 1001 Broadway Seattle, Washington 98122. Meets quarterly.

WEST VIRGINIA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. J. Dennis Kugel, 510-517 Med. Arts Bldg. Charleston, W. Va. 25301. Meets concurrently with annual meeting of West Virginia State Medical Society; other meetings arranged by program committee.
WESTCHESTER COUNTY RADIOLOGICAL SOCIETY

Secretary, Dr. Edgar Palmer, 650 Main St., New Rochelle, N. Y. 10801. Meets on third Tuesday of January

and October and on two other dates.

Wisconsin Radiological Society, Chapter of ACR Secretary-Treasurer, Dr. Robert E. Douglas, 1209 S. Commercial St., Neenah, Wis. 54956. Meets twice a year, May and September.

WYOMING RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. J. D. Grant, Memorial Hosp., Sheridan, Wyo. Meets in fall with State Medical Society and in spring on call of President.

## Mexico, Puerto Rico and Central America

Asociación Costarricense de Radiología

Secretary, Dr. Jorge Vargas Segura, Apartado 5367, San José, Costa Rica. Asociación de Radiologos de Centro America y PANAMÁ. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.

Secretary-General, Dr. Roberto Calderón, Calle Central

Oeste No. 218, Managua, Nicaragua, Central America. Meets annually in a rotating manner in the six countries. Asociación Puertorriqueña de Radiología

Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad de Radiología de El Salvador

Secretary, Dr. Julio Astacio, 5a Av. Nte. No. 434, San Salvador, Rep. El Salvador.

Sociedad de Radiología de Guatemala

Secretary, Dr. Carlos E. Escobar, 92. Calle A 0-05, Zona 1, Guatemala.

Sociedad Mexicana de Radiología, A.C.

Coahuila No. 35, México 7, D.F. Secretary-General, Dr. Bernardo Serviansky. Meets first Monday of each month.

SOCIEDAD RADIOLÓGICA PANAMEÑA

Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting. SOCIEDAD RADIOLÓGICA DE PUERTO RICO

Secretary, Dr. Heriberto Pagan Saez, Apt. 9387, Santurce, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

## BRITISH COMMONWEALTH OF NATIONS

Association of Radiologists of the Province of Que-BEC

Secretary, Dr. Pierre Archambault, Hôpital Charle Le Moyne, 121 Boul. Taschereau, Greenfield Park, P.Q., Canada. Meets four times a year.

BRITISH INSTITUTE OF RADIOLOGY

Honorary Secretary, Dr. G. H. du Boulay, 32 Welbeck St., London, W. 1, England. Meets monthly from October until May.

Canadian Association of Physicists, Division of Medical and Biological Physics.

Honorary Secretary Treasurer, Dr. R. G. Baker, Ontario Cancer Foundation, Ottawa Civic Clinic, 1053 Carling Ave., Ottawa 3, Ont., Canada. Annual Congress, to be announced.

EDMONTON AND DISTRICT RADIOLOGICAL SOCIETY Secretary, Dr. L. A. Koller, Suite 360, Professional Bldg., 10830 Jasper Ave., Edmonton 15, Alberta, Canada Meets third Thursday of each month October to May, except December, at various Edmonton Hospitals.

FACULTY OF RADIOLOGISTS

Honorary Secretary, Robert Morrison, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting, Oxford, England, July 2-3, 1971.

FACULTY OF RADIOLOGISTS, ROYAL COLLEGE OF SURGEONS

IN IRELAND

Registrar, Dr. H. O'Flanagan, F.R.C.P.I., D.P.H., 123 St. Stephens Green, Dublin 2, Ireland.
SECTION OF RADIOLOGY OF THE ROYAL SOCIETY OF MEDI-

CINE (CONFINED TO MEDICAL MEMBERS)

Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1, En-

CANADIAN ASSOCIATION OF RADIOLOGISTS

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## AFRICA

Association of Radiologists of West Africa

Honorary Secretary, Dr. S. B. Lagundoya, University
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Feb. 5-6, 1971, Conference Centre, University of Ibadan,
Ibadan, Nigeria.

South African International radiological Congress Director, Dr. Paul Sneider, P.O. Box 4878, Johannesburg,

South Africa.



## ABSTRACTS OF RADIOLOGICAL LITERATURE

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## ROENTGEN DIAGNOSIS HEAD

Benson, D. Frank, LeMay, Marjorie, Patten, David H., and Rubens, Alan B. Diagnosis of normal-pressure hydrocephalus. *New England J. Med.*, Sept., 1970, 282, 609–615. (Address: Dr. Benson, 150 S. Huntington Avenue, Boston, Mass. 02130.)

The term of Normal Pressure Hydrocephalus (NPH) has been extensively used to identify the syndrome of dementia, gait disturbance and incontinence in persons with enlarged ventricles and in whom there is no recorded evidence of elevated cerebral spinal fluid or ventricular pressure, but whose clinical symptoms are dramatically improved by ventricular shunting. The term communicating hydrocephalus denotes free communication between the subarachnoid space and the ventricles. In this group, however, some cases demonstrate easy flow of cerebrospinal fluid through the cortical subarachnoid channels, representing nonobstructive communicating hydrocephalus (hydrocephalus ex vacuo, central atrophy), whereas others do not, and can be regarded as obstructive communicating hydrocephalus. Whether NPH includes both these varieties or only the latter is at present under debate.

Although clinical evaluation of the patient is valuable, it is not diagnostic. Three laboratory studies have proved useful.

- (1) Normally, intrathecally administered RISA diffuses through the cerebrospinal fluid and radioactivity is demonstrated over the cerebral hemispheres and in the parasagittal area in 12 to 24 hours. Serial scans are obtained approximately 6, 24, 48, and, if necessary, 72 hours or more after injection. In normal studies none of the labeled material is detected in the ventricles in any of the scans. In hydrocephalus ex vacuo there may be some delay in isotope circulation, but RISA can usually be seen in the ventricular area at some time between 6 and 48 hours in sufficient concentration to produce an outline of the ventricle visible in both anterior and lateral views. In contrast to the pattern of isotope circulation in normal subjects and in nonobstructive communicating hydrocephalus, patients with NPH will show early ventricular filling. There is also a persistence of ventricular concentration, which contrasts sharply with the lack of appreciable activity over the surface of the hemispheres.
- (2) The pneumoencephalographic changes produced by NPH are usually diagnostic, but may be equivocal. The changes are reflected particularly in the lateral ventricles. As the ventricles enlarge, the most striking increase occurs in the anterior portion of the lateral ventricles. In those with normal sized ventricles, on anteroposterior roentgenograms with the patient supine, the superior margins of the lateral ventricles are obtuse, usually forming an angle be-

tween 130 and 140 degrees (corpus callosal angle). In communicating, nonobstructive hydrocephalus this angle often increases. In patients with NPH, however, the angle of the corpus callosum narrows. Eleven of the 12 patients in this study had a corpus callosal angle of 100 degrees or less.

(3) The angiographic changes produced by hydrocephalus are similar whether they are due to NPH or to an obstructive lesion in the posterior fossa.

Of the 12 cases, positive on both the intrathecal RISA scan and pneumoencephalograms, 7 were treated by ventriculoatrial shunt. Five showed improvement ranging from slight to dramatic. Two patients, both with large porencephalic cysts, continued to deteriorate after operation and died. Shunt was not performed in 3 patients because of unrelated disease and in 2 because they were demonstrating spontaneous improvement at the time the diagnosis was made.

Using these 2 procedures, it is possible to separate cases with obstructive communicating (NPH) and nonobstructive hydrocephalus. The former appeared to benefit from shunting of the ventricular cerebrospinal fluid, whereas the latter did not.—David Morse, M.D.

HARWOOD-NASH, D. C. Axial tomography of the optic canals in children. *Radiology*, Aug., 1970, 96, 367-374. (From: Department of Radiology, The Hospital for Sick Children, Toronto, Ontario, Canada.)

The author discusses the use of polytomography performed in the axial projection. The value of this examination is for complete visualization of the optic canals in their longitudinal axes. Both canals are visualized in their entire length on one film. In addition, there is evaluation of the anatomic structures adjacent to the canals and the sella—the lesser wings of the sphenoid, the anterior clinoids, the optic strut areas, and the planum sphenoidale, as well as the tuberculum sellae.

The author describes the normal values for canal dimension measurement and discusses canal shape and angulation. He indicates the range of the variation in size for children of different ages.

There is also a discussion of simultaneous tomography and pneumoencephalography.

The study encompassed 59 normal children of all ages for evaluation of normal and standard measurements. Sixteen abnormal cases were evaluated. These included 6 cases of optic nerve gliomas and 10 cases of parasellar mass lesions. In the study a maximum transverse diameter greater than 7 mm. was considered abnormal. The unilateral enlargement of one optic canal 1 mm. greater than the opposite was considered abnormal and was associated with optic glioma with the exception of 1 case. The difficulty in detecting gliomas on conventional roentgenograms is also mentioned.

The examination is easy to perform in children due to the ready facility for hyperextension to achieve the submento-vertex position.—J. P. Eberts, M.D.

SYME, JAMES. An unusual result from cross-compression in carotid angiography. Australasian Radiol., May, 1970, 14, 164–163. (From: Department of Radiology, University of Melbourne, Melbourne, Australia.)

A case is reported in which carotid angiography revealed an aneurysm of the supraclinoid portion of the internal carotid artery. Evaluation of cross-circulation was not achieved by needling the opposite carotid artery. The opposite common carotid artery was selectively catheterized and injection was performed with external compression of the initially injected carotid artery. Transient syncope, brady-cardia, and hypotension with a brief generalized epileptiform seizure resulted. The angiogram showed not only excellent cross-circulation, but also reflux of contrast medium into the basilar and both vertebral arteries—an unexpected finding in this 66 year old patient.

The author believes that this combination of findings was the result of a direct effect of the contrast medium associated with manipulation of the left common carotid bifurcation during external compression.—David Morse, M.D.

Gonzalez, Leopold, Mackenzie, Allen H., and Tarar, Riaz A. Parotid sialography in Sjögren's syndrome. *Radiology*, Oct., 1970, 97, 91–93. (From: Departments of Radiology and Rheumatology, Cleveland Clinic Foundation, Cleveland, Ohio.)

In a study of 63 patients with definite or probable Sjögren's syndrome, bilateral sialography with oily contrast medium demonstrated patterns of peripheral sialectasis in 59 (94 per cent) of the cases. Cy indirical peripheral ectasis was the most common roent-genologic finding present in 34 patients (55 per cent), second was punctate ectasis in 17 (28 per cent), with globular and fusiform changes present in 8 to 12 per cent of the cases. Only 1 case revealed cavitary changes. In 6 patients (10 per cent) cylindrical and fusiform changes in the primary branches appeared.

Only 3 cases revealed dilatation of Stensen's duct which was considered to be due to previous inflammatory change or incidental and not a feature of Sjögren's syndrome. Since the presence of acinar filling due to overinjection increases the time of the clearance of the contrast medium from the ducts in variable degree, abnormal retention was felt to be of relatively less diagnostic value.

It was concluded that cylindrical sialectasis represents a criterion for early diagnosis of Sjögren's syndrome and is valuable for confirming probable cases or for defining those in which the clinical laboratory pictures are questionable.—William L. Graham, M.D.

## ABDOMEN

BEECKMAN, P., VAN MOL, D., and VAN DE VELDE, E. Duodénographie hypotonique sans sonde duodénale. (Tubeless hypotonic duodenography.) J. belge de radioi., 1970, 53, 256–265. (From: Service de Radiodiagnostic, Université de Gand, Gand, Belgium.)

After discussing the various methods which have been proposed to achieve hypotonic duodenography (introduction of Antrenyl or Xylocaine by catheter, use of atropine, probanthine, etc.) the authors propose the following routine:

The contents of I ampoule of Visceralgine "Forte" and 0.5 mg. of atropine sulfate are mixed in a syringe, and the needle placed in an antecubital vein. With the table elevated to 45°, barium is given and when it enters the 2nd portion of the duodenum the drug is injected, the table leveled and spot filming done rapidly, as the duodenum becomes hypotonic in about 10 seconds and remains so for 2 to 4 minutes only.

This simple procedure permits superior study of 3 types of lesions: (1) disease of the ampulla of Vater and the pancreas; (2) postbulbar ulcers; and (3) antrobulbar lesions.—Frank A. Riebel, M.D.

Rossi, Plinio, and Gould, Howard R. Angiography and scanning in liver disease. Radiology, Sept., 1970, 96, 553-562. (From: Department of Radiology, St. Vincent's Hospital and Medical Center of New York, N. Y.)

The authors review 105 cases examined by both liver scans and selective celiac or hepatic arteriograms, where proof of diagnosis was obtained by needle biopsy, laparotomy, or postmortem examination in 77 cases. They describe their arteriographic and scanning techniques.

The 77 proven cases were divided into 3 categories: (1) space-occupying masses; (2) cirrhosis; and (3) normal. There were 26 space-occupying masses; of these, scanning was positive in 81 per cent and arteriography in 88 per cent. One or the other was positive in 92 per cent. In 35 proved cirrhotic patients, the scan was positive in 81 per cent, the arteriogram in 91 per cent.

The characteristic findings in space-occupying lesions and in cirrhosis on arteriography and on scanning are discussed.

The conclusion is reached that: (1) scanning and arteriography are complementary to each other; (2) angiography provides better anatomic delineation of the lesion and may show smaller lesions; and (3) angiography is necessary to determine if true neoplasms coexist with cirrhosis.—Carl H. Weidenmier, M.D.

BOLLAERT, A., LAMBILLIOTTE, J. P., DAGNELIE,

J., and Pector, J. C. L'hépatographie transombilicale. (Transumbilical hepatography.) J. belge de radiol., 1970, 53, 266–285. (From: Services de Radiodiagnostic et de Chirurgie, de l'Hôpital Universitaire St. Pierre, Bruxelles, Belgium.)

Catheterization of the umbilical vein can be accomplished under local anesthesia through a 2-3 cm. incision made half-way between the xiphoid and umbilicus. The round ligament is identified in the preperitoneal fat and a catheter is advanced upward into the vein; the last centimeter of the latter is little more than a fibrous septum, but when this is perforated there is immediate reflux of portal blood. Thirty to 50 ml. of urografin (60 or 76 per cent) is injected rapidly by hand, after small injections under fluoroscopic control have confirmed proper placement of the catheter.

Hepatography comprises 2 phases: a portal phlebogram lasting for 4-5 seconds; and a sinusoidal phase from about the 4th to the 10th second; 2 or 3 films per second are exposed during this period.

The authors performed transumbilical hepatography in 34 cases and found it to be useful in identifying metastases, hepatomas, invasions by hydatid cysts, cirrhosis of the liver, and to exclude diagnosis of liver abscess; in 2 cases they demonstrated that the abscesses were actually perihepatic and subphrenic rather than hepatic. Portal pressures could be determined in cases of cirrhosis as a part of the procedure. Suprahepatic veins have been occasionally identified, although the opaque medium is too dilute there to permit precise conclusions.

The authors consider the technique to be easier and less dangerous than splenoportography, as there is no danger of bleeding, and portal vein visualization is distinctly superior. In certain cases it can replace arteriography of the celiac trunk for localization of intrahepatic masses.—Frank A. Riebel, M.D.

BERK, ROBERT N. Changing concepts in the plain film diagnosis of ruptured spleen. J. Canad. A. Radiologists, June, 1970, 21, 67-70. (From: University of California, San Diego School of Medicine, La Jolla, Calif.)

Celiac arteriography is now considered the proper method to make an immediate and accurate diagnosis of ruptured spleen. Formerly, plain film studies of the abdomen had an important role in the diagnosis of splenic injury. At the present time, the concept is that the plain film studies need only suggest necessity for arteriography.

The author has reviewed a series of 25 patients in whom the diagnosis of ruptured spleen was established preoperatively by celiac arteriography. He then, in retrospect, reviewed the plain film findings and he noted that classical plain film x-ray findings

of ruptured spleen were present in only 20 per cent of the cases.

He emphasizes that bleeding into the peritoneal cavity occurs early and that this bleeding can be determined or suspected by watching the most dependent portion of the peritoneal space which is the pouch of Douglas on either side of the rectum above and behind the bladder. He points out that as the volume of fluid increases, it later collects laterally in the flanks and displaces the ascending or descending portions of the colon medially. He believes that when the presence of blood can be established, surgery is indicated without preoperative confirmation by arteriography. This is true unless multiple visceral injuries are suspected.

The conclusion offered is that the mere suspicion of blood in the pouch of Douglas or in the flanks on either side is sufficient indication to proceed with celiac arteriography. The diagnosis can then be made quickly and surgery can be carried out before there is any major loss of blood.—Richard E. Kinzer, M.D.

## GENITOURINARY SYSTEM

Speirs, C. F., Thomson, W. N., and Murdoch, J. McM. The predominance of right renal and ureteric pyelographic changes in patients with recurrent urinary tract infections. *Brit.* J. Urol., Aug., 1970, 42, 393-397. (Address: C. F. Speirs, M.B., Lilly Research Centre Ltd., Windlesham, Surrey, England.)

Utilizing the roentgenologic features considered compatible with a diagnosis of pyelonephritis (localized or generalized calyceal blunting with or without cortical scarring, discrepancy of more than 1.5 cm. in renal length, or dilatation of the ureters), the authors studied 460 female patients, mainly adults, with urinary tract symptoms or asymptomatic bacteriuria who demonstrated these features. Of these, 258 showed right-sided abnormalities, 60 showed left-sided abnormalities and 142 showed bilateral abnormalities. This held true through all ages (1-70 years).

Right-sided abnormalities were 3 to 5 times commoner than on the left regardless of parity, 3 to 9 times commoner regardless of the duration of history of urinary tract symptoms, and 3 to 12 times more frequent irrespective of time of onset of urinary symptoms or a symptomatic bacteriuria.

Of those patients with significant bacteriuria, 264 had abnormal urographic features of pyelonephritis. Right-sided abnormalities (121) predominated over left-sided (46), but bilateral abnormalities (97) were almost as common as right-sided lesions.

Vesicoureteral reflux occurred in 78 of 174 voiding cystograms, 53 per cent with right-sided reflux, 24 per cent with left-sided reflux and 23 per cent with bilateral ureteral reflux.

Compression of the ureters during intravenous

urography commonly caused temporary blunting of the right calyces, but only rarely on the left.

Since infection alone (hematogeneous or ascencing pyelonephritis) might be expected to cause bilateral lesions, the authors conclude that there are anatomic and physiologic differences between the ureters which might be responsible for the predominantly right-sided lesions. A fluid-filled cecum and terminal ileum might transmit external compression to the right ureter. Pregnancy appears to accentuate this by affecting the underlying anatomic and physiologic variations between the two ureters. It is possible that even minimal intermittent lower urinary tract obstruction is responsible for some of the roentgenologic features associated with chronic pyelonephritis, usually with bacterial infection but possibly in some cases without infection.—Richard C. Pfister, M.D.

Collard, M., and Brasseur, P. Le diagnostic radiologique de l'abcès périnéphrétique. (The radiologic diagnosis of perinephric abscess.) J. belge de radiol., 1970, 53, 291–299. (Address: Dr. M. Collard, 6110 Montignies-le-Tilleul, Belgium.)

Perinephric abscesses develop in 1 of 3 ways: from a renal lesion extending either directly or by perihilar lymphatics; from an extrarenal cause (septic metastases, spreads from gastroduodenal, pancreatic or colic disease); or by tearing of a calyceal or papillary membrane from increased pressure; these usually occur in tissue already made fragile by an infectious process.

The radiologic findings lag behind clinical signs because the outline of the kidney is little affected and the extensive retroperitoneal spaces permit large accumulations of fluid before either the kidney outline or collecting patterns change. Therefore, when symptoms persist the intravenous study should be repeated under televised fluorography with a special search for contrast medium which passes directly from a calyx to a perirenal lodgement. Tomographic examination should be included.

Studies should be repeated until the outlines are proved to be consistently normal, and in the exceptional case even beyond that, for a gross subcortical lesion may escape ordinary observations, only to be revealed clearly by selective arteriography.—Frank A. Riebel, M.D.

STEWART, B. H., DUSTAN, H. P., KISER, W. S., MEANEY, T. F., STRAFFON, R. A., and Mc-CORMACK, L. J. Correlation of angiography and natural history in evaluation of patients with renovascular hypertension. J. Urol., Aug., 1970, 104, 231–238. (From: Cleveland Clinic Foundation, Cleveland, Ohio.)

Since Goldblatt's work in 1934, many techniques

have been developed to detect occlusive renal vascular disease, and surgical procedures for correction have been developed. Recently it has been recognized that there are several different kinds of renal vascular disease and that each of these has a specific microscopic pattern and a specific radiographic appearance. The authors point out that each also has its own natural history, making it possible to predict the future with some degree of accuracy.

Based on a study of 201 patients undergoing surgery for renal vascular hypertension between 1964 and 1968, and on a second group of 88 patients who were followed conservatively, the authors have developed "a philosophy of management for each type of renal vascular disease."

Atherosclerosis predominantly in men and in older age groups, usually occurs in the proximal 2 cm. of the renal artery. The lesion involves the intima and in two-thirds of the cases, there is an eccentric plaque. In the other third, the vessel is involved circumferentially and in many of these cases dissecting hematomas result in thrombosis of the entire vessel. This disease is common and comprises 60 per cent of the total number of patients studied. On the basis of the cases studied it is advisable to operate only on good risk patients with recent onset of hypertension. In those patients with long standing hypertension the disease will not progress in about two-thirds of the cases.

Intimal fibroplasia cannot be distinguished radiographically from fibromuscular hyperplasia. This lesion is seen in children and in young adults. The lumen of the artery is compromised and vascular reconstruction should be done because the disease may subsequently develop in the opposite renal artery. The disease tends to progress and surgery should be carried out as soon as a diagnosis can be made.

Fibromuscular hyperplasia carnot be distinguished radiographically from intimal fibroplasia and usually there is smooth stenosis of the renal artery or its branches. Because it is progressive in nature, it should be managed as intimal fibroplasia and young patients should be operated on immediately with revascularization procedures.

Medial fibroplasia, occurring mostly in women of middle age, is the most common of the fibrous lesions and has formerly been classified as fibromuscular hyperplasia, but this is not true since there is no muscular hyperplasia present. Radiographically the typical string of beads pattern is seen. This is produced by fibrous rings interspersed with short segments of aneurysmal dilatation. Microscopically, both destruction and thickening of the media are seen in alternating areas. Radiographically, this lesion is usually extensive and involves the distal two-thirds of the main artery and extends into the branches in about a third of the cases. Multiple aneurysms are characteristic and they are greater in diameter than the normal renal artery proximal to

the disease. On the basis of the patients studied, the philosophy of management indicates that recent onset, good risk patients should be operated on with revascularization technique. The disease seems to burn itself out and patients more than 40 years old can frequently be treated medically without fear of progress of the disease.

Subadventitial fibroplasia in young women and involving renal arteries only, is a tightly stenotic lesion. Islands of smooth muscle are occasionally trapped within collagenous rings. The appearance of beading is seen on the arteriogram. The authors point out that the caliber of the normal segment of the vessel is not exceeded by the bead and this makes it possible to differentiate the lesion from medial fibroplasia in which the aneurysmal dilatations have a diameter much greater than the diameter of the renal artery. This is a rapidly progressive disease and most of these patients should be treated surgically. The lesions are focal in nature and resection with re-anastomosis of the vessel can usually be accomplished.

The article is nicely illustrated with radiographic and pathologic demonstrations of each type of disease.—Richard E. Kinzer, M.D.

TABERN, D. L., KEARNEY, J., and SOHN, H. The quantitative measurement of tubular chlormerodrin binding as an index of renal function: a study of 400 cases. Canad. M. A. J., Sept., 1970, 103, 601-607. (Address: Dr. D. L. Tabern, Radioisotope Laboratories, Louis A. Weiss Memorial Hospital, 464 Marine Drive, Chicago, Ill. 60640.)

The authors describe a new quantitative method of ascertaining renal tubular function. This is determined by measuring the renal uptake of Hg<sup>203</sup> chlormerodrin at 4 hours, since stabilization of the count rate is complete at this interval.

Based on the 4 hour renal chlormerodrin uptake in 400 patients the authors have correlated the uptake values with clinical renal function.—Richard C. Pfister, M.D.

GRAY, W. The effect of osmotic diuresis on the radio-isotope renogram in ureteric obstruction. *Brit. J. Urol.*, Aug., 1970, 42, 425–428. (Address: Bridge of Earn Hospital, Bridge of Earn, Perthshire, England.)

Although the diagnostic value of radioisotope renography in obstructive uropathy is well established, it has not been possible to distinguish the renographic pattern of severe ureteric obstruction from that of hydronephrosis associated with lesser degrees of obstruction or obstruction which has been relieved. I<sup>151</sup>-hippuran renogram was studied before and during a forced diuresis (mannital or frusemide) in 57 patients with ureteral obstruction.

Comparison of the paired renographic tracings taken before and during osmotic diuresis showed that the delay in the excretory phase either remained unchanged (23 patients) or became considerably less marked (34 patients). Exaggeration of the obstructive pattern during the increase in urine flow was not observed. The majority of patients with an unchanged excretory phase had an acute obstruction of the ureter from calculus, while in those patients whose renograms improved during the diuresis the obstructive uropathy was from hydronephrosis without evidence of ureteral calculus. There was no difference in the mean rate of urine flow between these two groups.

The author concludes that improvement in the renogram is attributed to decrease in upper urinary tract stasis secondary to increased urine flow with forced diuresis. This suggests a milder degree of ureteric obstruction or residual dilatation of the upper tract.—Richard C. Pfister, M.D.

Warren, Michael M., Kelalis, Panayotis P., and Utz, David C. The changing concept of hypernephroma. J. Urol., Sept., 1970, 104, 376–379. (From: Section of Urology, Mayo Clinic and Mayo Foundation and the Mayo Graduate School of Medicine, University of Minnesota, Rochester, Minn.)

Hypernephroma was described by Grawitz in 1883 and this disease has been studied and discussed at great length since that time. The diagnosis was made in the early years on the basis of flank pain, hematuria, and a palpable abdominal mass. In order to study the evolution of hypernephroma, the authors have taken a series of 400 patients seen at the Mayo Clinic from 1961 through 1967 and have compared this series with a similar Mayo Clinic series seen from 1940 to 1950. These 400 patients are also compared with other reported groups to try to determine whether there is a changing clinical picture. Only 166 patients had urinary complaints, while 234 patients did not have urinary complaints. Thirtyeight per cent of the Mayo Clinic patients had socalled systemic symptoms including fever, weight loss, fatigue and anorexia. There were 20 per cent of the Mayo Clinic patients who had no symptoms. Sixty-four per cent of the patients in the present Mayo Clinic series had low hemoglobin levels and 66 per cent had elevated sedimentation rates.

Sixty per cent of the series had abnormalities in hepatic function. These abnormalities cannot be taken to represent hepatic metastasis. The liver function tests were reversible and in many of the postoperative cases all tests did return to normal. When preoperative liver function tests are abnormal, repeat studies postoperatively should be of some value since return to normal or near normal levels after operation indicates that there has been complete resection of malignant tissue. However, there have

been some patients whose liver function tests returned to normal postoperatively, but then became abnormal at a later follow-up date. All of these patients had local spread or distant metastasis, or both.—Richard E. Kinzer, M.D.

## SKELETAL SYSTEM

ADLER, JACK J., and SHARMA, OM P. Hypertrophic osteoarthropathy with intrathoracic Hodgkin's disease. Am. Rev. Resp. Dis., July, 1970, 102, 83-85. (From: Lincoln Hospital and Department of Medicine, Albert Einstein College of Medicine, New York, N. Y., and the Department of Medicine, Royal Northern Hospital, London, England.)

Hypertrophic osteoarthropathy is manifested by clubbing of the fingers and toes and proliferative periostitis of the long bones. It is seen less often in the metacarpals, metatarsals and proximal phalanges. The etiology is unknown. It may be accompanied by pain, edema and vasomotor disturbances. It is generally associated with disease of the lungs or heart, although occasionally no underlying disease can be found. Rarely is it seen in Hodgkin's disease. It has not previously been reported in a child.

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The authors conclude that the clubbing might be an important clue to the development of pulmonary lesions in patients with Hodgki Heiser, M.D.

Herndon, James H., and Co. Chondroma of a lumbar ver child: an unusual tumor res doma. J. Bone & Joint Su 52-A, 1241-1247. (Address: don, M.D., 300 Longwood . Mass. 02115.)

A case of chondroma of a lumb in a child is reported. The chohistologic characteristics suggest Chondroma of the spine is rare and embryologic implications in this report.

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The embryologic explanation for explored; the uniqueness of the the rare location are emphas Young, M.D.

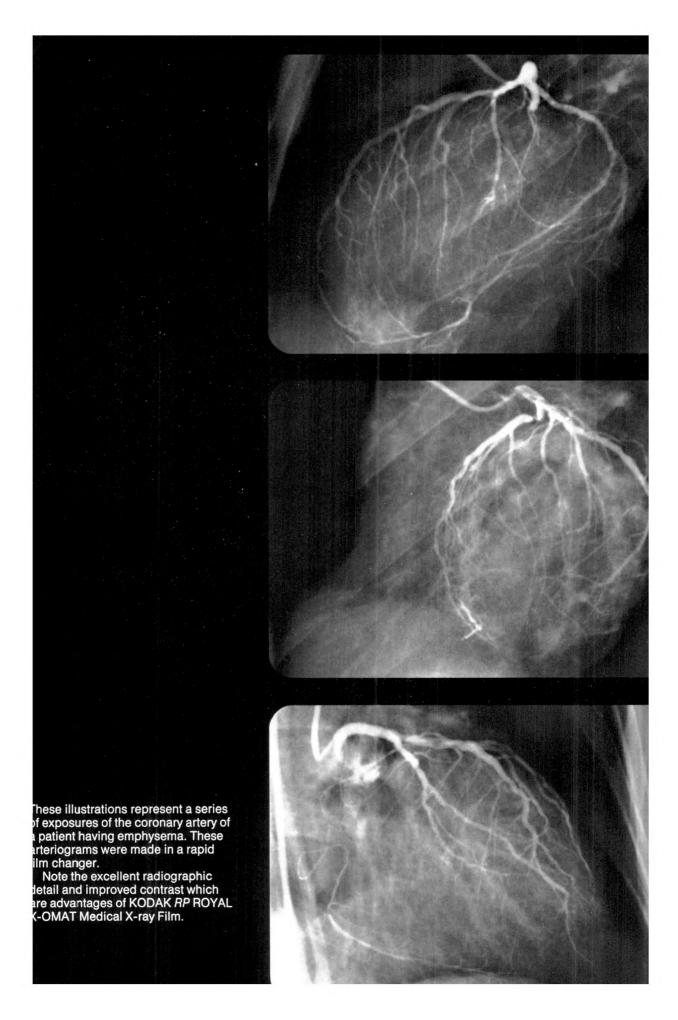


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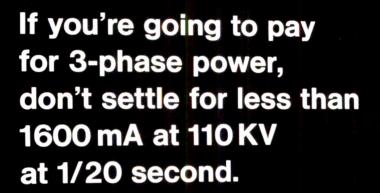
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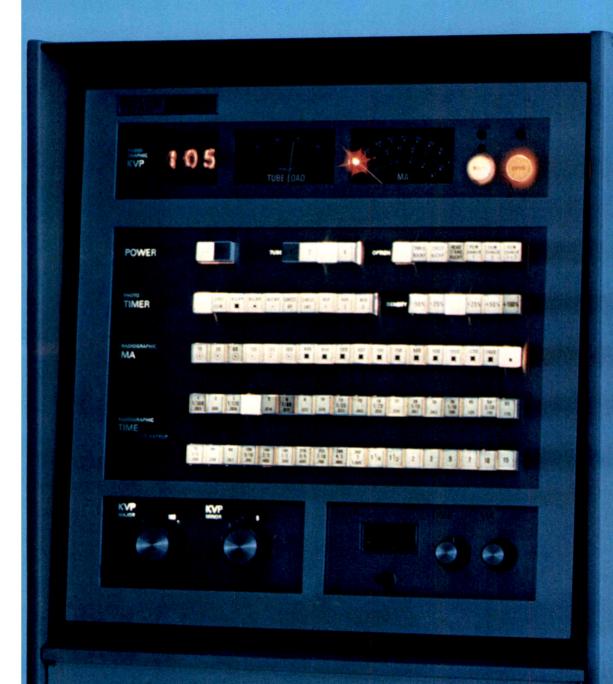


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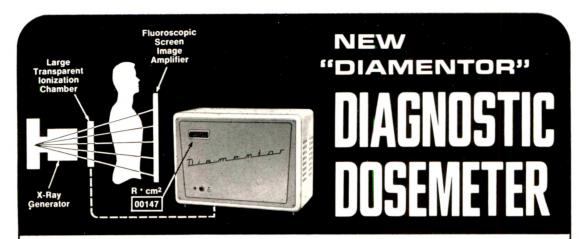
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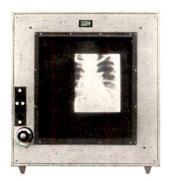
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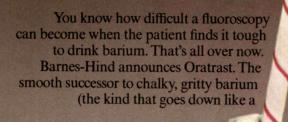
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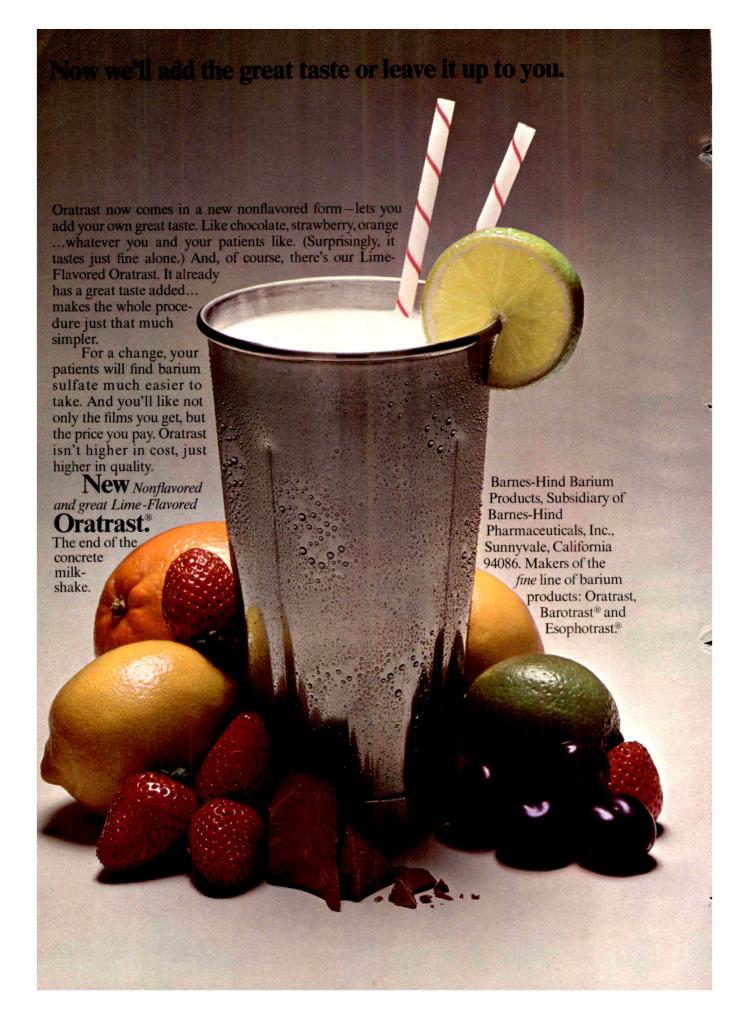
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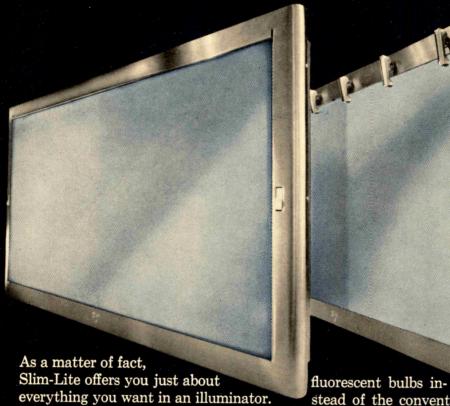
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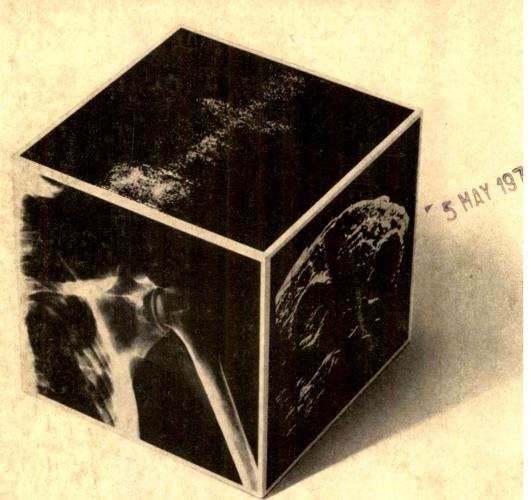
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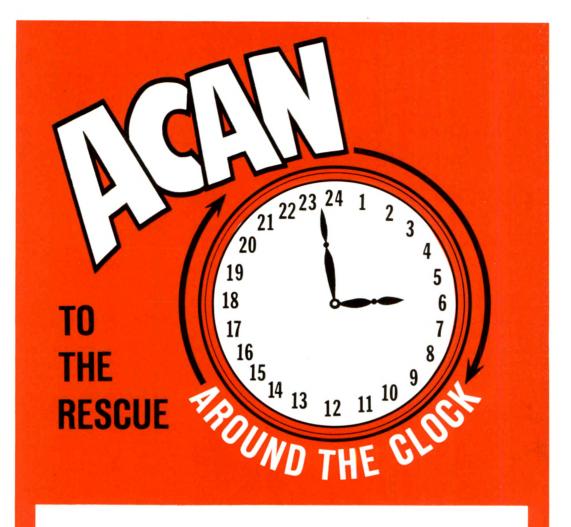
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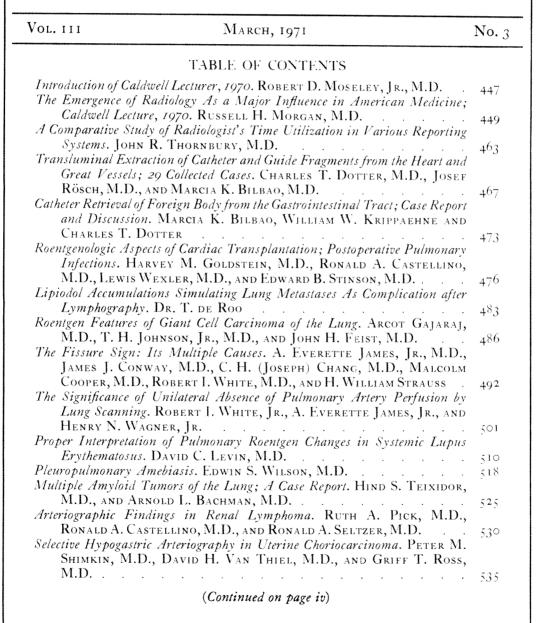
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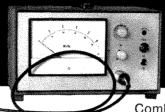
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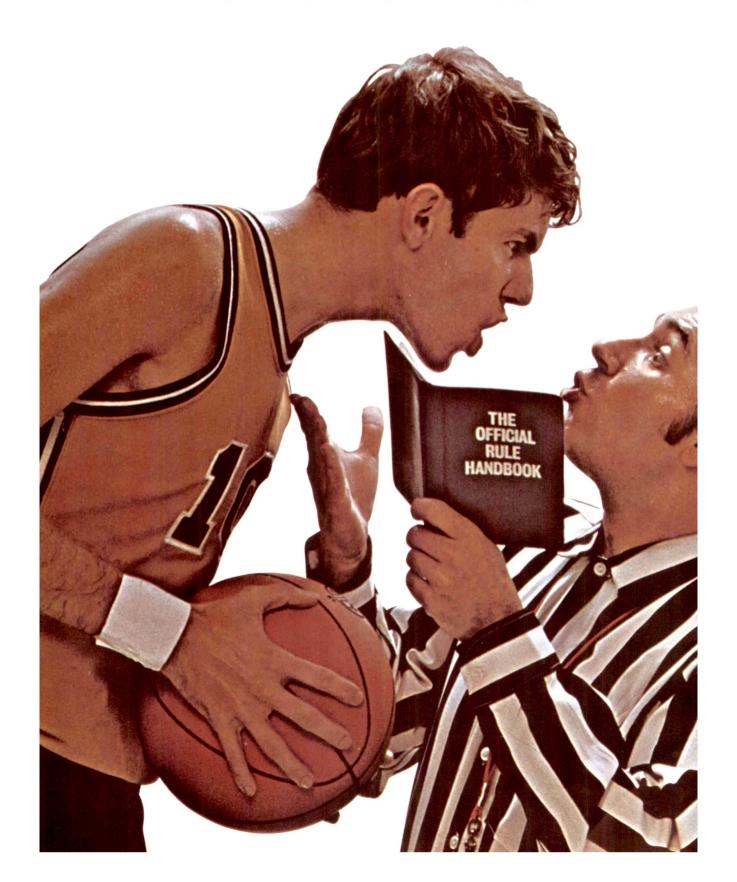
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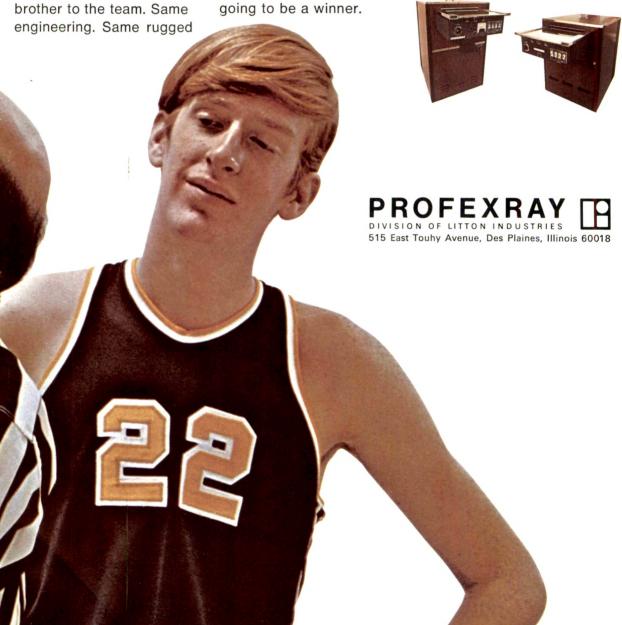
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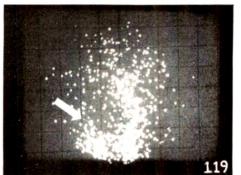
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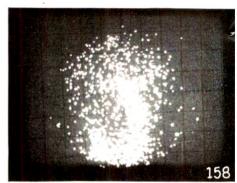
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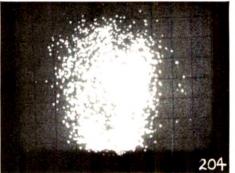
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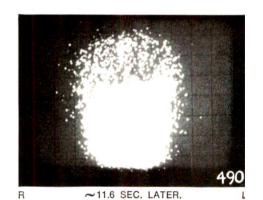
R ~3.4 SEC. FOLLOWING INITIAL DETECTION OF ABNORMALITY ON PERSISTENCE SCOPE.



R ∼1.2 SEC. LATER.



R ~2.7 SEC. LATER. L



STATIC SCINTIPHOTO.
ANTERIOR VIEW.

RIGHT OBLIQUE
VIEW.

THE PHO/GAMMA
SCINTILLATION CAMERA.

## h C r bral "Fl:.w" -t::dv

#### Evaluation of Cerebral Vascular "Flow" with the Nuclear-Chicago Pho/Gamma® Scintillation Camera

In this technique using 99mtechnetium pertechnetate for dynamic study of vascular "flow" pathways (both intra- and extra-cranially), the Pho/Gamma Scintillation Camera is equipped with the Nuclear-Chicago Super-8/Persistence Scope.

SETTING-UP. The standard 4000 parallel-hole collimator is used. The area to be visualized includes the patient's neck and head. With the patient in the supine position, the Pho/Gamma detector is positioned touching the tip of the nose. This orientation can be readily achieved, because of the Pho/Gamma detector's positioning flexibility.

ISOTOPE AND DOSE. An intravenous injection of 10 mC of 99mtechnetium pertechnetate is administered. preferably in one of the antecubital veins. No attempt is made for a bolus injection.

DATA ACCUMULATION AND DISPLAY. At the first detection of events on the persistence scope (which displays data in live "fluoroscopic" fashion), the scope display is filmed with the Super-8 movie camera. Frame rate is 32 per second. Filming is stopped when the recirculation phase is detected — usually about one minute after the beginning of the study.

Then, approximately one hour later, conventional scintiphotos are taken, in a variety of viewing positions, each representing approximately 250,000

The motion-picture film is subsequently viewed with the Super-8 Analyst projector in slow, fast, or stopmotion, as necessary for evaluation.

These Pho/Gamma-generated data can also be recorded, in high-resolution digital form, on the Nuclear-Chicago Data-Store/Playback Accessory or on the CDS-4096 Clinical Data System. With either of these system accessories, patient data can be stored and then re-played, processed, and manipulated at the clinician's discretion. The result is an increased range of analysis, yielding additional qualitative and quantitative data.

CASE HISTORY. The clinical study illustrated on the opposite page is of a patient with the following history: Male, 51 years old. Three-month history of intermittent episodes (one to three minutes duration) of right visual-field constriction. Physical examination negative, except for slight blurring of right optic disc.

EVALUATION. In the selected frames from the Super-8 motion-picture film shown at left, these clinically relevant indications are seen: Frame 119, there is no isotope flow through right carotid artery pathway (arrow); note also outline of anterior and middle cerebral artery pathways, with relatively decreased concentration in right hemisphere. In Frame 158 (capillary phase), block in right carotid pathway is still evident. In Frame 204 (venous phase), delayed arterial perfusion in the right hemisphere begins. And, in Frame 490, recirculation with evident delayed arterial perfusion in right hemisphere is seen.

The static scintiphoto shown is essentially negative for any evidence of abnormal isotope accumulation, as were a number of other scintiphotos taken following the Super-8 study.

CONCLUSIONS. In this case, detection and localization of an abnormal "flow" pattern in the Super-8 dynamic study—but not in the static scintiphotos—led to a meaningful differential diagnosis. To this end, a serial arteriographic study was performed. The radiograph selected from that study reveals complete occlusion (arrow) of the right internal carotid artery at the bifurcation with the external carotid on the right. The intra-cranial problem was therefore shown to be the result of extra-cranial pathology.

Thus the Pho/Gamma Scintillation Camera permits the use of a relatively innocuous, yet rapid, technique to produce supplementary diagnostic information. This information can provide direction for the use of other investigative techniques and make possible a more definitive diagnosis.

#### **Nuclear Reviews**

WHAT'S A CDS-4096? That's our Clinical Data System. For image-data storage from the Pho/Gamma. In digital form. For a variety of displays and manipulation. Write for the CDS-4096 brochure.

THE PLACE FOR IN-VITRO COUNTING. It could be in your lab. Because gamma counting, in-vitro, is the way to go at times. We make it easy. Ask us for details on our gammacounting systems.

An exchange of information on topics



which has more than a passing interest in

# If you know get to know



#### Triosorb-125 T-3 Diagnostic Kit\*

The in vitro test unmatched for reproducibility, convenience and accuracy.

Reproducible. Over 15 million tests conducted over the past eight years have made Triosorb® the standard of T-3 tests.

Convenient. The disposable Triosorb® Kit is ready for immediate use at room temperature making it one of the simplest, most convenient thyroid function tests available.

Accurate. Approximately 15 drugs and conditions produce misleading Triosorb®-T-3 test results, compared with over 200 factors which affect PBI.



#### Tetrasorb-125 T-4 Diagnostic Kit

An improved, simplified method for measuring total *serum* thyroxine with diagnostic accuracy equal to or better than any currently used measures of thyroid function. Unlike other tests, exogenous iodines don't affect Tetrasorb® results.

<sup>\*</sup> Also available as Triosorb®-131.

one of these, them all.



## The T-7 value completes the thyroid profile.

It's the Abbott method for determining the in vitro free thyroxine index.

T-7 is not a test but a numerical value derived from the multiplication of T-3 and T-4 test values. Because it is a product of two other numbers, the *T-7 value* will *move* only when both the T-3 and T-4 values move in the *same direction*. There are *only* two physiological conditions which cause this to occur, *hypothyroidism* and *hyperthyroidism*. With the exception of those patients receiving liothyronine or d-thyroxine therapy, all other factors which affect thyroid function tests will cause the T-3 and T-4 values to move in opposite directions, and the T-7 value to remain in the normal range.

When you provide the Abbott T-3, T-4 and T-7 values you furnish a complete thyroid profile with unparalleled clinical accuracy.

## With LOGIC<sup>™</sup> your final step is as easy as 1,2,3.

- 1. Establish a baseline.

  Pre-set count for 10,000; read the required time from the NIXIE tubes.
- 2. Take a post-wash reading.

  Pre-set *timer* for the baseline established in step 1.
- 3. Read the percentage uptake directly from the NIXIE tubes.

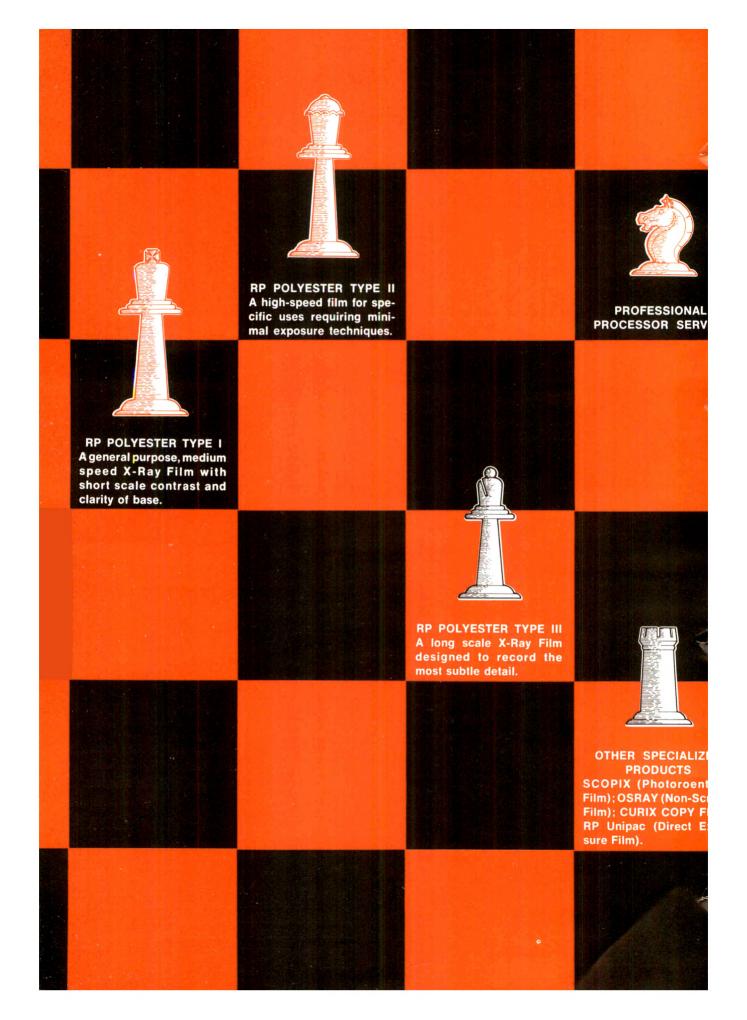
  LOGIC™ provides direct ratio readout in percentage.

No conversions or calculations needed. Minimal chance for error.

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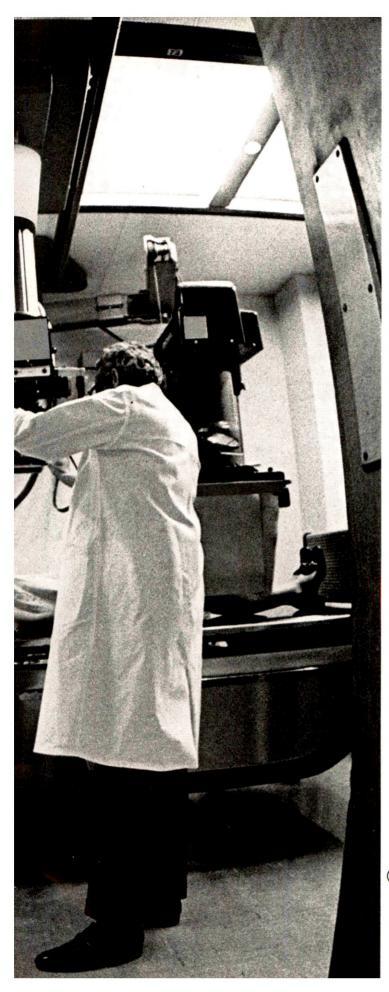
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When you want speed <u>and</u> detail, there's no equivalent for Radelin's STF-2, the <u>fastest X-ray</u> <u>screen available</u>. Radelin puts 50% more phosphor on the screen, to gain a 65% reduction in patient exposure — compared to par speed — and <u>without any significant</u> loss of detail.

In addition to its speed, STF-2 is easier to clean and keep clean. It has high static resistance, high moisture resistance, dimensional stability and uniformity of speed and performance from screen to screen.

With Radelin STF-2 screens there's no need to compromise! Call your supplier today.

#### Rādelin STF-2

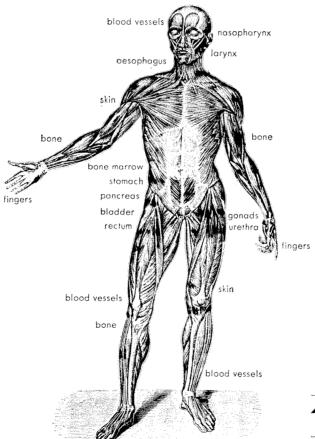
The fastest X-ray screen available.

For total performance . . . use Radelin screens and Halsey cassettes.

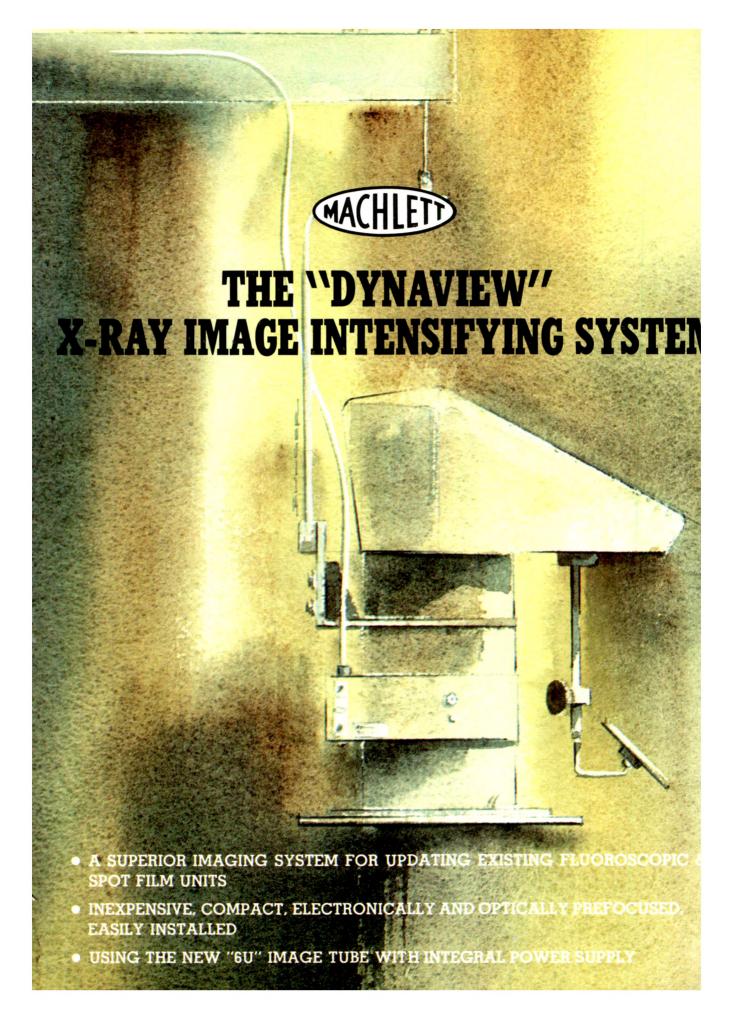


#### ISOTOPES TLD-THE ONLY DOSIMETRY SYSTEM YOU NEED.

Now, for the first time there's a single system of measurement for almost all human dosimetry problems - ISOTOPES TLD. With Phosphor-Teflon TLD dosimeters in rod, disc and tape form - in vivo and external radiation can be readily measured. Micro-rods have been used for intracavitrary and interstitial dosimetry. For depth dose measurements, diagnostic roentgenography, nuclear medicine and personnel monitoring, disc dosimeters are employed routinely. All of these dosimeters can be quickly and easily read out on ISOTOPES versatile TLD Readout Instrument. Or our simplified, low-cost, portable Berkeley reader. For complete information about this new single radiation measurement system, call or write ISOTOPES, 50 Van Buren Avenue, Westwood, New Jersey 07675 (201) 664-7070.







## THE "DYNAVIEW" IMAGE INTENSIFYING SYSTEM

The DYNAVIEW imaging system has been developed to fill the need for an easily installed inexpensive unit to replace the conventional fluoroscopic screen in spot filming equipment or standard medical fluoroscopes. The basic model consists of an image tube and housing with integral power supply, a mirror viewer, a compact universally adaptable ceiling suspension unit and an interchangeable plate to fit in place of the fluoroscopic screen.

The Dynascope "6UC" image tube, housing, and solid state integral power supply has been selected as ideal for this system due to its outstanding performance. It provides maximum brightness, excellent resolution and contrast. The DYNAVIEW system can also be supplied with the new Dynascope "6U" tube, a dual mode tube where the central 4" of the input image can be electronically expanded to provide a magnified image. The tube will be shipped with its solid state power supply in the same housing and with the focusing voltages preadjusted and preset. This concept completely eliminates the need for high voltage cables, and means that the tube will be focused at the factory under laboratory conditions. Thus the only electrical connection required for the DYNAVIEW system is to a 115 volt 50 or 60 cycle supply.

To further simplify the installation of this unit the major component of the optical system will be permanently mounted and prefocused.

The ceiling suspension system which is provided to counterbalance the weight of the tube, power supply and optical system is designed to provide travel along the length of the fluoroscopic table through the installation of new ceiling rails, if required, or by using existing ceiling rails. (Various adapters are available for most types of ceiling rails.) The suspension unit itself provides for cross table movement.

The bottom of the image tube housing is designed to be attached to properly rayproofed plates built to fit various types of spot film devices. These plates are designed so that the image tube and viewer can be easily removed from the fluoroscopic screen frame if necessary.

The unique concept of the DYNAVIEW system, its simplicity of installation, its low cost, and its high quality make it possible for the first time to consider the use of image intensifying techniques to replace all fluoroscopic examinations.

Available through your x-ray equipment dealer.





Someone must be sure of something.\*

PICKER





#### Over 1000 examinations by 18 investigators prove the efficacy of drip infusion pyelography

### **RENO-M-DIP**<sup>™</sup>

Meglumine Diatrizoate Injection U.S.P. (30%-For Drip Infusion Pyelography)

The diagnostic effectiveness of drip infusion pyelography has been established in over 1000 radiologic examinations of individual patients by 18 independent investigators.<sup>1</sup>

In a composite of the 1,062 patients studied and reported upon, 87% showed excellent to good urograms. In these studies, 728 patients received a 1:1 dilution of a 60% solution of meglumine diatrizoate, and 334 received the ready-to-use 30% solution.

These studies also showed that not only are dense nephrograms obtained with the drip infusion pyelography procedure, but satisfactory cystograms are also provided. In addition, pictures of the ureter were definitive—usually with complete visualization on one film.

Drip infusion pyelography was used successfully even in cases with various degrees of azotemia—and in many instances was shown to avoid the need for retrograde pyelography.

#### Better visualization

Improvement over regular I.V. pyelography was shown specifically in 89.5% of 180 cases by 8 of the 18 investigators.<sup>1</sup>

#### Adverse reactions

Adverse reactions were generally mild and occurred in 6.7% of the cases. The most frequent reactions were nausea and urticaria (see brief summary on next page). (All meglumine diatrizoate solutions used were equivalent to 30% concentration.)

#### A convenient bottle

The bottle containing Reno-M-DIP is calibrated, to make dosage measurement easy. It has a standard screw-neck that accommodates all the usual attachments. It will take any top—screw-top, needle or spike. Drip infusion pyelography is a simple, reliable, and relatively safe procedure for diagnosis of urologic disease process. Use Reno-M-DIP whenever drip infusion pyelography is indicated.

1. Data on file at The Squibb Institute for Medical Research. See next page for brief summary.

#### **SQUIBB**

'The Priceless Ingredient of every product

## Whenever drip infusion pyelography is indicated

#### RENO-M-DIP

Meglumine Diatrizoate Injection U.S.P. (30%-For Drip Infusion Pyelography)

Reno-M-DIP<sup>TM</sup> (Meglumine Diatrizoate Injection U.S.P.) for drip infusion pyelography provides a sterile, aqueous solution of 30% meglumine diatrizoate which contains approximately 14% (42.3 grams per 300 cc.) bound iodine and 0.04% disodium edetate as a sequestering agent. The solution contains approximately 0.054 mg. (0.002 mEq.) sodium per cc. (16.2 mg. per 300 cc.).

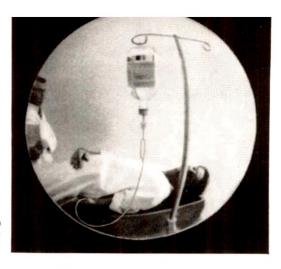
Contraindications: Contraindicated in persons hypersensitive to salts of diatrizoic acid. Urography is contraindicated in patients with anuria.

Warnings: A definite risk exists with the use of contrast agents in excretion urography in patients with multiple myeloma. There has been anuria with progressive uremia, renal failure and death. This risk of the procedure in these patients is not a contraindication; however, partial dehydration in preparation for study is not recommended since it may predispose for precipitation of myeloma protein in renal tubules. No therapy, including dialysis, has been successful in reversing this effect. Myeloma should be considered in persons over 40 before undertaking urographic procedures.

In cases of known or suspected pheochromocytoma, if the physician feels that the possible benefits outweigh the considered risks, radiopaque materials should be administered with extreme caution; however, an absolute minimum of material should be injected, the blood pressure should be assessed throughout the procedure, and measures for treating a hypertensive crisis should be available.

Contrast media may promote sickling in homozygous individuals when injected I.V. or intra-arterially. Although a history of sensitivity to iodine *per se* or to other contrast media is not an absolute contraindication, administration of meglumine diatrizoate requires extreme caution in such cases. Meglumine diatrizoate should be used in pregnant patients only when the physician deems its use essential to the welfare of the patient since safe use during pregnancy has not been established. Perform thyroid function tests prior to administration of meglumine diatrizoate since iodine-containing contrast agents may alter the test results. Perform urography with extreme caution in persons with severe concomitant hepatic and renal disease.

Precautions: Diagnostic procedures involving use of contrast agents should be performed under the direction of personnel with prerequisite training and a thorough knowledge of the particular procedure. Appropriate facilities should be available for coping with situations which may arise as a result of the procedure and for emergency treatment of severe reactions to the contrast agent itself; competent personnel and emergency facilities should be available for at least 30 to 60 minutes after I.V. administration since delayed reactions have been known to occur. These severe life-threatening reactions suggest hypersen-



sitivity to the contrast agent. A personal or family history of asthma or allergy or a history of a previous reaction to a contrast agent warrants special attention and may predict more accurately than pretesting the likelihood of a reaction although not the type nor severity of the reaction in the individual. The value of any pretest is questionable. The pretest most performed is the slow injection of 0.5-1.0 cc. of the preparation which may be given through the needle to be used for the full dose. If no reaction occurs within 15 minutes, the full dose may be given; however, this does not preclude the possibility of reaction. Should the test dose produce an untoward response, the necessity for continuing the examination should be reevaluated. If deemed essential, examination should proceed with all possible caution. In rare instances, reaction to the test dose may be extremely severe; therefore, close observation and facilities for emergency treatment are indicated.

Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by urographic agents; therefore, if known or suspected hepatic or biliary disorder exists, administration of meglumine diatrizoate should be postponed following the ingestion of cholecystographic agents. Consider the functional ability of the kidneys before injecting meglumine diatrizoate.

The recommended rate of infusion should not be exceeded. The diuretic effect of the drip infusion procedure may hinder an assessment of residual urine in the bladder. Adequate visualization may be difficult or impossible in uremic patients or others with severely impaired renal function (see Contraindications).

Adverse Reactions: Reactions most frequently encountered with drip infusion pyelography are nausea and urticaria. Chills, metallic taste, vomiting, dizziness, a rise or fall in blood pressure, itching, flushing, or generalized feeling of warmth, sneezing, etc. may occur and, rarely, may be severe enough to require discontinuation of dosage. Severe reactions which may require emergency measures (see Precautions) are a possibility and include cardiovascular reaction characterized by peripheral vasodilatation with hypotension and reflex tachycardia, dyspnea, confusion, and cyanosis progressing to unconsciousness. An allergic-like reaction ranging from rhinitis or angioneurotic edema to laryngeal or bronchial spasm or anaphylactoid shock may occur. Temporary renal shutdown or other nephropathy may occur. Intravenous injection of meglumine diatrizoate in a more concentrated formulation has produced a few instances of a burning or stinging sensation and of venospasm or venous pain.

Supply: Bottles of 300 cc. © 1971 E.R. SQUIBB & SONS, INC

SQUIBB The Priceless Ingredient of every product is the honor and integrity of its maker.

## Clysodrast® (bisacodyl tannex)

the colonic evacuant containing tannic acid and bisacodyl

SEE NEXT PAGE FOR COMPLETE PRODUCT INFORMATION.

## **Clysodrast**<sup>®</sup>

(bisacodyl tannex)

#### A COLONIC EVACUANT

#### Description:

Each packet of CLYSODRAST contains 1.5 mg. of 4,4'- (diacetoxydiphenyl) - (pyridyl - 2) methane complexed with 2.5 Gm. of Tannic Acid, N.F., in a readily soluble form.

#### **Actions:**

CLYSODRAST is a non-absorbable colonic evacuant which provides good cleansing of the colon when used as an enema. The tannic acid serves to solubilize the 4,4'-(diacetoxydiphenyl) - (pyridvl - 2) - methane as well as to inhibit the secretion of the secretory glands in the colonic mucosa. Tannic acid contained in CLYSODRAST is watersoluble and precipitates protein. Its astringent effect inhibits secretion of mucus in the walls of the large intestine.

#### Indications:

CLYSODRAST (bisacodyl tannex) may be indicated for the preparation of patients for radiologic examinations of the colon, sigmoidoscopy and proctologic examinations.

#### Contraindications:

CLYSODRAST is contraindicated in patients under the age of 10 because the possibility of absorption of tannic acid has not been adequately studied in this age group to warrant a conclusion of safety. CLYSODRAST is also contraindicated in cases with known or suspected extensive ulcerative lesions of the colon.

#### Warning:

#### Usage in Pregnancy

Safe use of CLYSODRAST has not been established with respect to the adverse effects upon fetal development. Therefore, it should not be used in women of child-bearing potential, particularly during early pregnancy, except where, in the judgment of the physician, the potential benefits outweigh the possible hazards.

#### **Precautions:**

CLYSODRAST should be used with caution in a regimen where multiple enemas have been administered. Certain patients, because of age, debility, or underlying disease, require more gentle preparation than the routine castor oil and CLY-SODRAST (bisacodyl tannex) preparation. It is important that the instructions for preparation and administration be followed in detail, and that the recommended dosages not be exceeded.

#### Adverse Reactions:

The following adverse reactions have been reported: Cramping, weakness, nausea and fainting.

#### Dosage and Administration:

It is important that the entire medical history and condition of the patient be considered in deciding the dosage regimen. Traumatizing procedures, such as repetition of enemas (with or without CLYSODRAST) should be kept at the minimum necessary to achieve the desired result.

#### Cleansing Enema

Prepare the cleansing enema by dissolving the contents of one packet (2.5 Gm.) of CLYSODRAST in one liter of lukewarm water and administer.

Prepare the barium enema by dissolving the contents of one or not more than two packets (2.5) Gm. or 5.0 Gm.) of CLYSODRAST in one liter of barium suspension. If more than one liter of barium suspension is prepared, it is important that the concentration of CLYSODRAST (bisacodyl tannex) never exceed 0.5 percent (2 packets per liter).

The total dosage of CLYSODRAST for any one complete colonic examination, including the cleansing enema, should not exceed 7.5 Gm. (3) packets). No more than 10 Gm. (4 packets) of CLYSODRAST should be administered to any individual within a 72-hour period.

#### Preparation of the Patient:

#### General Procedure

On the day prior to examination, the patient is placed on a residue-free diet. Castor oil, one to two ounces, is administered approximately 16 hours before examination. On the day of examination, the CLYSODRAST cleansing enema is given (see "Dosage and Administration") and expelled. Results are inspected and if a considerable amount of fecal material is present in the toilet bowl, the enema may be repeated.

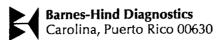
Routine Barium Enema — In addition to the general procedure outlined above, good evacuation of the barium sulfate enema may be obtained by adding CLYSODRAST to the suspension as described under "Dosage and Administration."

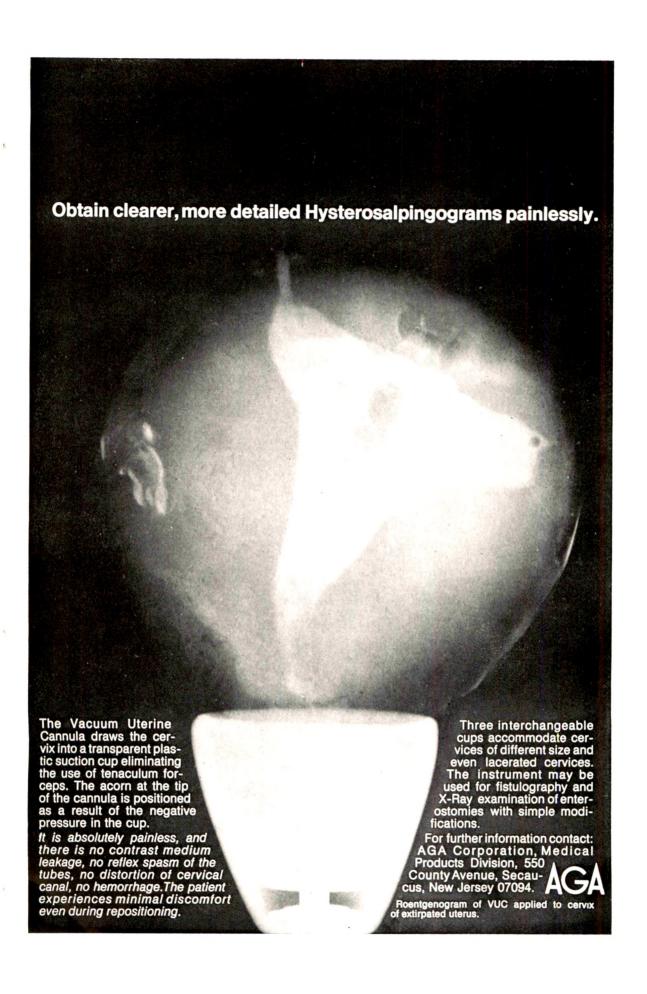
Double-Contrast Studies — Only barium sulfate which is specially processed and specially designed for this purpose should be used. In addition to the "General Procedure" as outlined above, CLYSODRAST (bisacodyl tannex) may be added to the barium sulfate suspension. The CLYSODRAST serves in eliminating the excess radiopaque medium. After evacuation, a uniform deposition of the contrast substance remains on the colonic mucosa. The patient is then ready for the introduction of the air.

#### **How Supplied:**

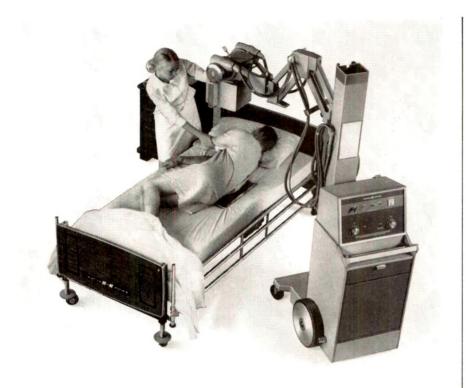
CLYSODRAST is supplied in packets containing 1.5 mg. of 4,4'- (diacetoxydiphenyl) - (pyridyl - 2) methane and 2.5 Gm. of Tannic Acid, N.F. These packets are supplied in cartons of 25 and 50 packets.

Literature available on request





## information compendium



#### **CORDLESS MOBILE X-RAY UNIT:**

Tests demonstrate capability for obtaining procedure room film quality at bedside.

Two separate comparisons have verified the radiographic quality produced by General Electric's CMX-110,™ a cordless mobile x-ray unit powered by nickel-cadmium cells.

At a leading 500-bed university hospital, CMX-110 was tested along with two capacitor-discharge units and two systems utilizing single and 3-phase power. The object was to determine whether, in new construction, doctors could eliminate expensive high-power electrical outlets in patient rooms, operating areas and intensive care units and still obtain the desired film quality using currently available mobile x-ray units.

CMX-110 radiographs were described as "very satisfactory in terms of overall density and con-

trast under maximum radiographic demands." The conclusion was to eliminate the wiring in question and let CMX-110 handle the full range of radiographic needs outside the radiology department.

General Electric tests support this conclusion. Chest radiographs, of the same patient under identical conditions, proved CMX-110's effective x-ray output comparable to that produced in a system powered by a polyphase, 700 mA generator. Also, chest and abdomen films with a CMX-110 demonstrated distinct advantages in density, contrast and reliability to those produced by a popular capacitor-discharge unit under the same conditions.

Complete details of each comparison are available on request.

#### DIAGNOSTIC X-RAY SYSTEM:

Remote control of multi-function capability provides new answers for patient-load problems.

A total-remote diagnostic x-ray system, that makes it unnecessary for the radiologist to return to tableside during any procedure, has been introduced by General Electric.

The multi-function Telegem<sup>TM</sup> 90 permits fluoroscopy, radiography and tomography procedures in one room. Featured are 90°-90° table angulations and powered top movements that include vertical travel.

Multi-directional tubehead angulations permit oblique angle fluoroscopy of obscured areas, such as the sigmoid colon, and inaccessible structures. For scanning, the under-table image intensifier moves through 20 inches, to follow a single barium swallow down the esophageal tract.

Telegem 90 also features remote serialographic programming of multiple Bucky radiographic views, with up to six uniform images on a single film. The system accepts, and automatically centers, cassette sizes up to 14x17 inches, with automatic masking to format.





#### X-RAY TUBES:

Power-match tube and generator for maximum technic capability.

A heavy-duty x-ray tube, with the highest instantaneous exposure ratings available, heads General Electric's new line of Maxiray tubes. Three models match the power capability of every sized generator, for today's emphasis on high-energy and high-volume radiography.

The Maxiray 125 features a 125 mm (5 inch) diameter anode. All three models, including the 100 and 75, incorporate GE's exclusive composite Polyrhenium<sup>TM</sup> anode processing. This enables Maxiray tubes to store and dissipate the high heat levels generated during such procedures as rapid-film radiography, cine fluorography, spot-filming and extended schedules. Higher instantaneous exposure ratings permit greater radiation through a smaller focal spot for better image detail and resolution.

Maxiray tubes also provide greater performance stability at high kVp, a lower rate of radiation fall-off and longer tube life.

#### X-RAY GENERATORS:

Combine millisecond interrogation and 2-millisecond phototiming.

Two new General Electric MSI<sup>TM</sup> generators feature millisecond interrogation; exposures initiate and terminate instantly. Phototimed exposures are accurate down to two milliseconds.

When integrated into a diagnostic x-ray system, MSI generators make it possible to rapid-film at 12 frames per second and get 35 millisecond exposures. MSI generators also make lower kV values practical at 6 and 12 frames per second, while maintaining maximum film quality.

The MSI-1250 model generates 1200 mA and 150 kVp; the MSI-850 generates 800 mA and 150 kVp. Each delivers constant power, low-ripple D.C. output, even under high instantaneous loads.



#### **IMAGE INTENSIFIER:**

Totally-new system adds information potential to every image.



General Electric Company has introduced a new image intensifier that produces maximum clarity, brilliance and information content in every intensified fluoroscopic image. The Fluoricon® 300's unique optic system shortens the path the image travels before being displayed, and assures precise information transfer from the patient.

For improved filming capability, Fluoricon 300's new Cine 180

system doubles the useful recording area of 16 mm film and features frame rates up to 240 per second.

The cine pulse width automatically adjusts for optimum film density. After selection of the upper pulse width limit, optimum kV, mA and focal spot size, proper light levels must reach the film or the pulse rate automatically compensates.

The image presentation is also enhanced by a new TV chain, with automatic antivignetting. And, the three recording and display cameras — cine, photospot and TV — can be simultaneously mounted to the optical distributor.

Fluoricon 300 also features a choice of 9-inch single field or dual field image tubes; solid-state integrated circuitry throughout.

General Electric Medical Systems, Milwaukee, Toronto, Liege



# The new Picker/Vertex 35mm analytical projector:

# it neither looks nor acts like any cineprojector you've ever seen.

The Picker/Vertex 35mm analytical projector provides flickerless, high intensity projection of any black and white or color 35mm cinefilm up to 1,000 feet long, on any style spool or reel, with multiple safeguards against film damage. And:

**Big-screen projection** $-5\frac{1}{2}$ ′ x  $6\frac{1}{2}$ ′ image at approximately 16′ with "movie house" brightness.

**Flickerless projection**—at all speeds in forward or reverse, including single framing.

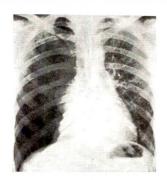
Five step speed selection—1% to 30 FPS and indefinite single-frame "hold" (without film damage).

Remote control of all operations—including coarse and fine focus, frame speed, and direction.

**Plus**—adjustable direction of projection, quiet operation, solid-state circuitry.

**More information?**—simply contact your local Picker representative or write Picker Corporation, 595 Miner Road, Cleveland, Ohio 44143.

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# A new series of manuals to teach the interpretation of roentgenograms

Squire, Colaiace & Strutynsky:

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Vol. 5: NUCLEAR MEDICINE
Vol. 6: PEDIATRIC RADIOLOGY

By Lucy Frank Squire, M.D., Harvard Medical School and Mass. General Hospital; William M. Colaiace, M.D., Brown Univ. and Roger Williams

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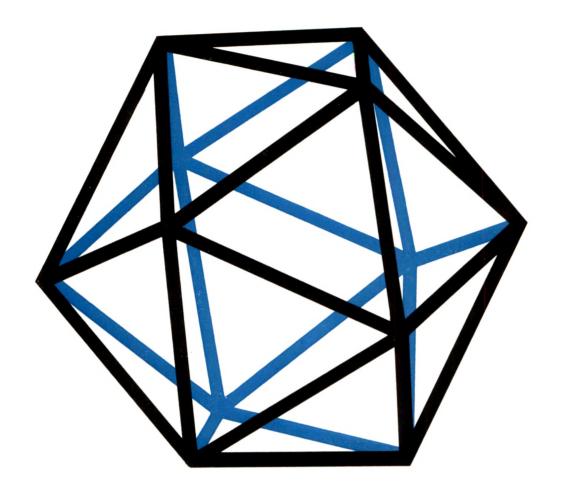
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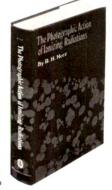
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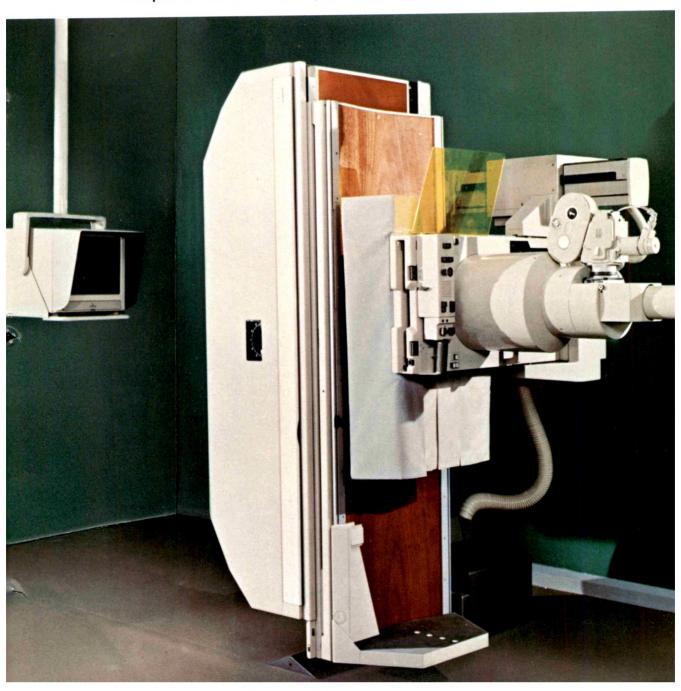
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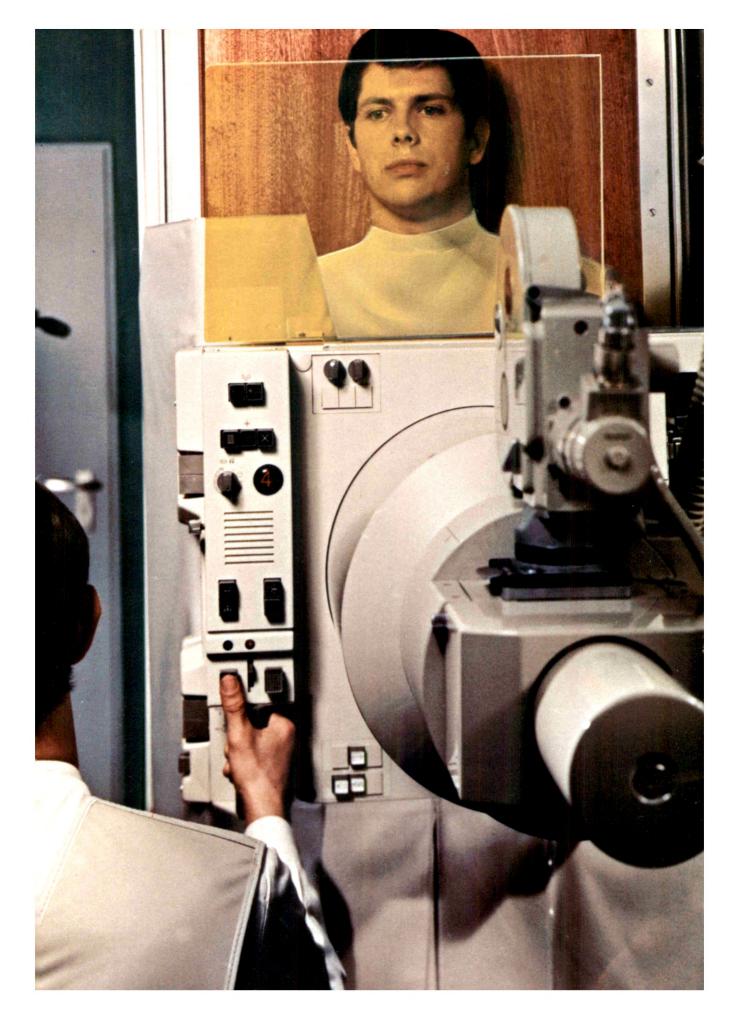




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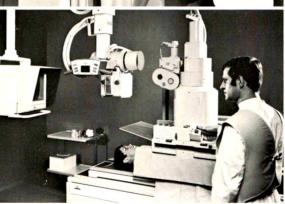
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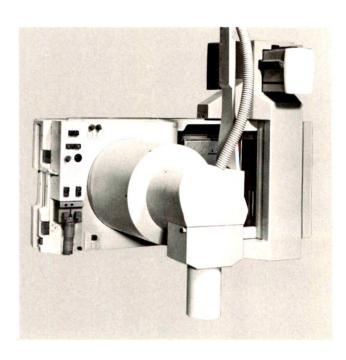
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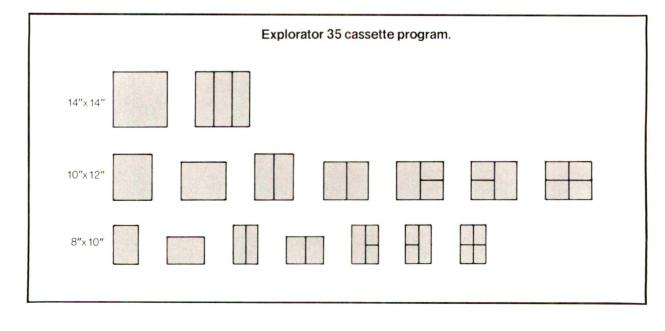
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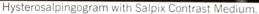


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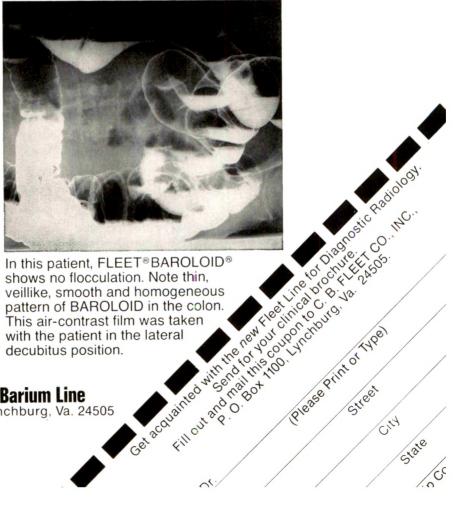
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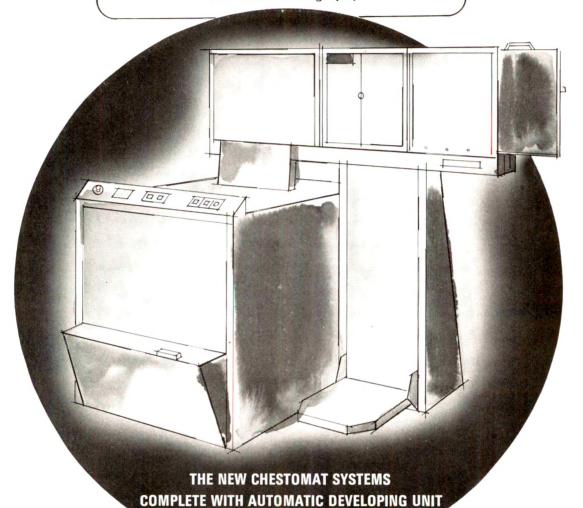
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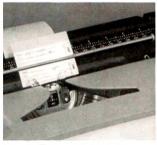
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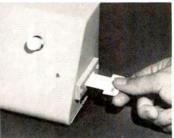
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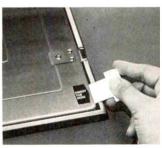
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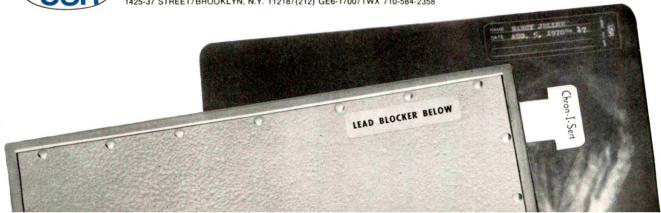


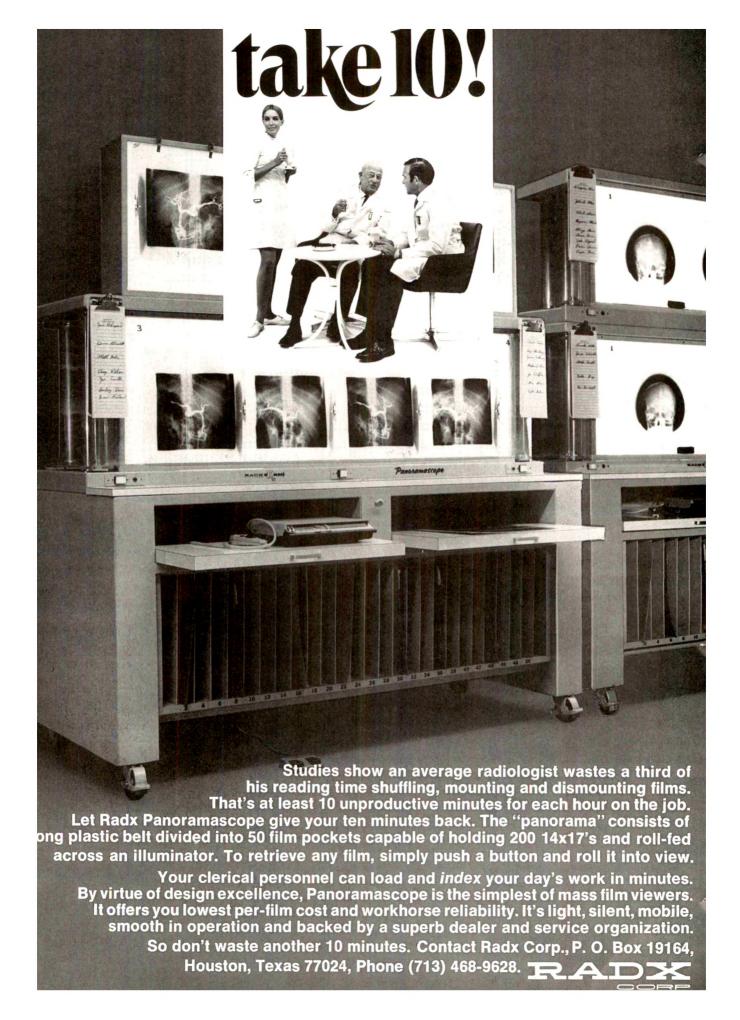
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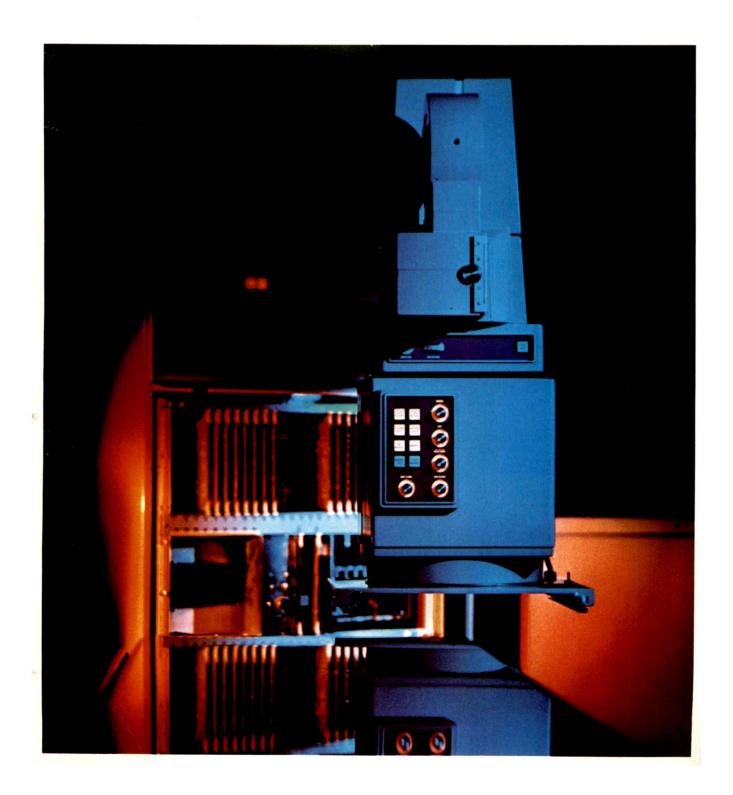
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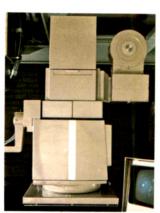
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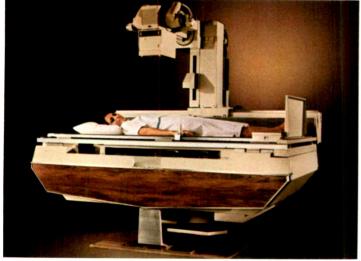
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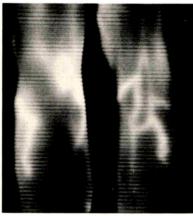
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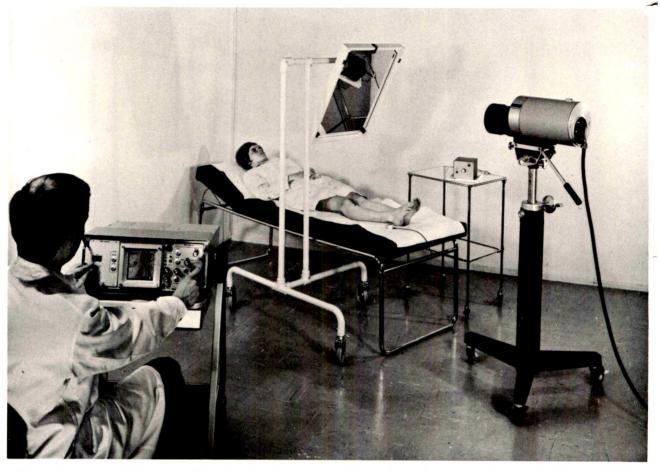


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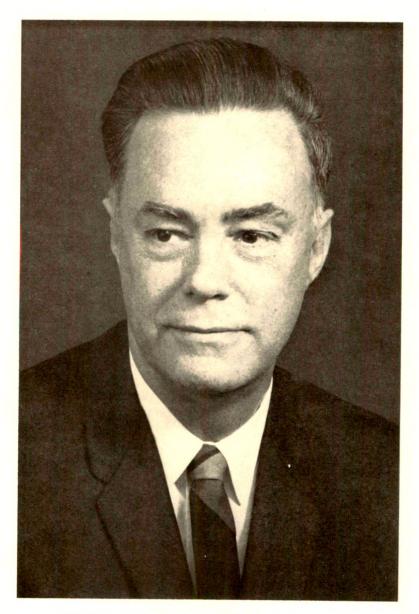
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# THE AMERICAN JOURNAL OF ROENTGENOLOGY

# RADIUM THERAPY AND NUCLEAR MEDICINE

Vol. III

MARCH, 1971

No. 3

### INTRODUCTION OF CALDWELL LECTURER, 1970\*

By ROBERT D. MOSELEY, JR., M.D. CHICAGO, ILLINOIS

"An honorable and revered friend, speaking of the favorable reception of my volumes, even in the circles of fashion and elegance, said to me, 'You have made them all talk Johnson.'—Yes, I may add, I have Johnsonized the land; and I trust they will not only talk, but think, Johnson." From Boswell's LIFE OF JOHNSON

I am honored to have been chosen to present the Caldwell Lecturer to you this evening. I believe that I am beginning to occupy with him the biographical relationship of Boswell to his Johnson. In February 1967 I had the privilege of presenting a record of his distinguished scientific contributions when he received the Gold Medal of the American College of Radiology. In August 1969 I shared with Dr. Paul C. Hodges the joy of presenting him for the Honorary Degree of Doctor of Science, bestowed upon him by The University of Chicago. Next month I will introduce him as the recipient of the Grubbe Medal of the Chicago Medical Society at a meeting of the Chicago Roentgen Society; and this evening I have the pleasure of introducing Dr. Russell Hedley Morgan for the Caldwell Lecture of the American Roentgen Ray Society.

Dr. Morgan is Professor and Chairman of the Department of Radiology, The Johns Hopkins University School of Medicine; Radiologist-in-Chief, The Johns Hopkins Hospital and Professor and Chairman of the Department of Radiological Sciences, The Johns Hopkins University School of Hygiene and Public Health. He is a meticulous and dedicated scientist, a careful and imaginative administrator, a gifted statesman with a distinguished record of service to Radiology, and, I am delighted to say, a great and good friend.

He developed the photoelectric timing concept and mechanism for the automatic control of roentgenographic exposure. His other major contributions have concerned themselves predominantly with many aspects of the theoretical basis of diagnostic radiology. Many of his basic contributions have resulted in substantial technical advances by himself or others. His major theoretical work has been concerned with the analysis of the physical factors controlling the diagnostic quality of roentgen images. He studied screen intensification systems and their

<sup>\*</sup> Presented at the Seventy-first Annual Meeting of the American Roentgen Ray Society, Miami Beach, Florida, September 29-October 2, 1970.

limitations; this basic investigation led ultimately to the development of fluoroscopic screen intensifiers and the application of television techniques to diagnostic roentgenology. Throughout his career both his theoretical and technical work have had as a major basis the protection of the patient from unnecessary radiation. He has been nationally and internationally active in the development of radiation protection standards. His most recent scientific contributions have related to theoretical considerations of visual perception and to investigations of information theory. He has applied modulation transfer function analysis to roentgenographic systems and has devised a new and widely accepted theory of threshold visual perception.

He has been responsible for the training of a truly distinguished group of young radiologists whose efforts now and in the future will bestow honor on him as well as on themselves. His position as a statesman representing the radiological sciences in both national and international councils marks an additional area of distinguished performance. He serves on the International Commission of Radiation Protection and is Vice-president of the National Council of Radiation Protection and Measurement. He was the Chairman of the National Advisory Committee on Radiation, appointed by the Surgeon General of the Public Health Service, which presented three significant and far-reaching reports to the nation. These reports and his other continuing activities on the federal scene have had a significant impact on Public Health action in relation to the control of radiation hazards in the United States and in relation to protecting and improving health through the radiological sciences.

To paraphrase Boswell, I wish I could Morganize the land, and I trust you will not only talk, but think, Morgan. Now, like Boswell with Johnson, in his presentation of the Caldwell Lecture we have the opportunity to experience the "exuberant variety of his wisdom and wit"—Dr. Russell Morgan.

Professor and Chairman Department of Radiology The University of Chicago 950 E. 59th Street Chicago, Illinois 60637



4

# THE EMERGENCE OF RADIOLOGY AS A MAJOR INFLUENCE IN AMERICAN MEDICINE\*

### CALDWELL LECTURE, 1970

By RUSSELL H. MORGAN, M.D.

#### I. INTRODUCTION

IT IS perhaps unnecessary for me to chronicle for this audience the events which have taken place in the radiation sciences during the past seven and one half decades since Roentgen's momentous discovery of the x ray. Almost all of you have participated actively in this history. Nevertheless, I shall do so briefly so as to give historical background to the discussions which follow.

There are few scientific discoveries in the history of mankind that have generated scientific and public reaction so immediate and so great as Roentgen's. The possibility of using x rays in medical and surgical diagnosis was recognized at once. Within the first year after the announcement of the discovery, almost one thousand scientific papers and many textbooks on x rays were published. It is perhaps of some interest that in February of 1896, the *Journal of the American Medical Association* expressed the cautious opinion that x rays might be useful in the treatment of disease.

Medicine was, of course, not the only scientific discipline to benefit from Roentgen's discovery. The natural sciences profited as well. One of the most important consequences was the discovery of radioactivity by Becquerel in 1896, soon to be followed by the discovery of radium by Marie and Pierre Curie in 1898.

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The discoveries of Roentgen, Becquerel and the Curies were the forerunners of a long series of brilliant scientific achievements. In 1905, Einstein proposed that mass and energy are related by the now well known equation,  $E = mc^2$ . In 1911,

Rutherford proposed an atomic theory in which he suggested that the mass and positive charge of the atom are concentrated in a central nucleus. And in 1913, Bohr proposed an atomic model comprising a central nucleus with electrons moving in systematic orbits about it.

In 1919, Rutherford found that the nuclei of nitrogen atoms under certain experimental conditions of bombardment yielded positively charged particles which he named protons. He also observed that in this process nitrogen atoms are transformed into oxygen. This was the first experiment in which one element was artificially transformed into another, the first time the alchemist's dream was realized. In the next year, Rutherford postulated that atomic nuclei also include a fundamental particle approximately the size of a proton bearing no electrical charge. This particle he named the neutron. Twelve years later, Chadwick discovered the existence of this particle and in 1934, Fermi, bombarding uranium and other atoms with neutrons, observed many phenomena of artificial transmutation and radioactivity.

In 1939, Hahn and Strassman bombarded uranium 235 with neutrons and demonstrated the phenomenon of nuclear fission, a process accompanied by the liberation of additional neutrons and the release of substantial amounts of energy. This work was followed by the development of the uranium pile or reactor in which uranium undergoes fission in a self-maintaining controlled reaction.

The development of the nuclear reactor raised the curtain on the atomic age and

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made possible the production of large amounts of radioactive materials which soon found widespread use in medicine. It also ushered in the era of nuclear power and made possible the production of atomic weapons of unprecedented magnitude.

Simultaneously with the work in the physical sciences, there was intensive study of the biological effects of x rays and of the radiation emitted from radium. Certain neoplastic processes were found to regress strikingly following the application of these ionizing radiations. Late in the 1920s, it was discovered that relatively small doses of radiation to reproductive cells produce changes or mutations in succeeding generations of the irradiated species.

### II. THE GROWTH OF CLINICAL RADIOLOGY

It did not take many months after the discovery of the x ray for physicians to exploit its diagnostic and therapeutic potentials. Although early x-ray apparatus left much to be desired, it was evident from the beginning that radiological methods provided a superb means of demonstrating the gross pathological characteristics of disease without at the same time disturbing body function. Moreover, in many cases, the method provided the detailed information needed by the physician to determine optimal therapy. For example, the patient with pain and crepitation following an injury to the forearm could not only have the presence of a fracture demonstrated but the position of the fragments and the extent of the comminution as well, information of prime importance to the orthopedic surgeon in his care of the injury. The usefulness of x rays and radium in the treatment of disease was also recognized early. Although precise methods of measuring radiation dose came only much later, radiation techniques were applied near the turn of the century to the treatment of many lesions, particularly in the field of neoplastic disease.

In the years prior to World War II, a long list of increasingly complex techniques were developed to demonstrate the relationships between clinical signs and symptoms and their pathological basis. Primary emphasis was on the detection of abnormal morphology with essentially every organ system coming under scrutiny. All of the medical disciplines were involved.

By 1940, the extent to which radiological methods had been applied to the diagnosis of disease suggested to some that clinical radiology was approaching maturity and that further growth of the discipline could not be expected. However, a few years later, an event took place which had a profound influence on the course of radiology. By the application of techniques in electron optics, the image amplifier was born and with it a new dimension was added to the diagnostic process. For the first time, a broad range of abnormal physiological states could be investigated under fluoroscopic control and recorded on motion picture film. As a consequence, the use of x rays in the study of many disease states affecting the cardiovascular, respiratory, gastrointestinal and genitourinary systems was sharply expanded. In addition, image amplifier technology placed a new dependence of the physician on the radiologist. To exploit this technology, it was necessary for the radiologist to develop a new set of operative skills which brought him increasingly into the center of clinical decisions.

By the 1960s, the applications of the radiation sciences in medicine had become so extensive that clinical radiology could no longer be maintained as a single discipline. Separate diagnostic and therapeutic divisions emerged. Moreover, a number of diagnostic subdivisions came into view when radiologists began to specialize in such fields as pediatric radiology and neuroradiology and in the radiological aspects of cardiology.

All through the post World War II period, something else was happening. With the availability of a broad variety of radionuclides, produced by the nation's atomic energy program, the science of nuclear medicine came into being and quickly became one of the fastest growing of the medical disciplines. Its diagnostic techniques were

found to be particularly valuable because they provided quantitative as well as qualitative information on the nature and extent of pathological processes not obtainable by other means. The detection of pulmonary embolic phenomena, the quantitative evaluation of thyroid physiology and the quantitative determination of hepatic biochemical relationships represent a few of a long list of procedures, advantageously carried out by nuclear methods.

Although clinical radiology had its origin only a short time ago, it today constitutes one of the major forces in clinical medicine. To illustrate the extent to which this is true, a recent study by the U. S. Public Health Service has shown that currently well over 100,000,000 diagnostic x-ray examinations are carried out annually in the United States.<sup>4</sup> This represents on average the performance of I diagnostic procedure for every 2 individuals in the population each year.

The increasing influence of radiology on medical practice is also shown in a recent study in which the hospital records of 100 patients, admitted to the Johns Hopkins Hospital for the first time in each of the years 1945, 1950, 1955, 1960 and 1965 were reviewed. Cases, exclusive of newborns, were selected at random in each year and the final discharge diagnoses were recorded on each patient up to and including the third major diagnosis. Of the 500 cases studied during the 20 year period, 66% were examined radiologically and of these almost three quarters (73%) had one or more of their diagnoses established or confirmed by radiological methods. Moreover, these percentages have tended to become greater in recent years (Table 1). These data, of course, do not indicate the extent to which radiology beneficially influenced the clinical course of the patients studied. It may be assumed, however, that the benefits were substantial in most cases although, as we shall see later, this assumption may not always be valid.

Perhaps the most impressive evidence affirming the growing role radiology has

Table I

SUMMARY OF DIAGNOSTIC INFORMATION ON SAMPLE OF

500 PATIENTS ADMITTED TO THE JOHNS HOPKINS

HOSPITAL BETWEEN 1945 AND 1965

	1945-65	1965
No. of patients reviewed	500	100
No. of primary diagnoses recorded	921	174
No. of x-ray examinations performed	881	160
Percentage of primary diagnoses established or confirmed by		
x-ray studies	33	44
No. of patients x-rayed	328	64.
No. of primary diagnoses among	•	•
patients x-rayed	639	114
Percentage of primary diagnoses among x-rayed patients estab- lished or confirmed by		·
x-ray studies	48	68
Percentage of x-rayed patients with one or more primary diagnoses established or confirmed by	·	
x-ray methods	73	90

assumed in American medicine appears in data collected by the American Medical Association (Table II) which indicate that more graduates from American Medical schools now enter residency training in radiology than in such specialties as pediatrics, pathology, obstetrics and gynecology, ophthalmology, orthopedic surgery, and anesthesiology.<sup>8</sup>

Only in internal medicine and general surgery are there appreciably more.

Table II

DISTRIBUTION OF GRADUATES OF U.S. AND CANADIAN MEDICAL SCHOOLS ENTERING RESIDENCY TRAINING IN VARIOUS FIELDS OF SPECIALIZATION ON SEPTEMBER 1, 19688

Specialty	Per cent	
Internal Medicine	21.0	
General Surgery	18.4	
Psychiatry	9.7	
Radiology	8.0	
Pediatrics	7.0	
Obstetrics-Gynecology	5.1	
Ophthalmology	4.5	
Orthopedic Surgery	4.2	
Anesthesiology	4.1	
Pathology	3.5	

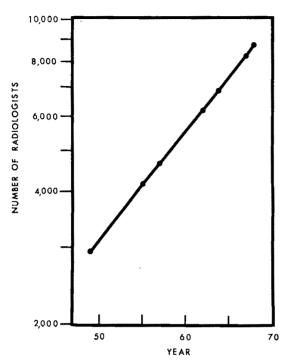


Fig. 1. Number of clinical radiologists, exclusive of residents in training, in practice in the United States.

# III. THE MANPOWER PROBLEM IN RADIOLOGY

As radiology has grown, the professional manpower pool which serves its needs has increased sharply. This is well shown in Figure 1, where the number of clinical radiologists, exclusive of those in training, is plotted for the past two decades. These data indicate an annual growth rate in radiological manpower of 5.7%, a rate sufficient to double the manpower pool every 12 years.

The distribution of this pool among the principal divisions of radiology has been quite uneven, reflecting the varied demands of the public for radiological services. In a study of 17 university hospitals in 1966, the National Advisory Committee on Radiation (NACOR) found that 72% of the professional manpower in radiology was then required to meet the needs of diagnostic roentgenology, 16% of radiation therapy and 12% of nuclear medicine (Table III). More recent studies indicate that no sub-

stantial change in this distribution has occurred in the intervening years.

What is the likelihood that the available professional manpower in radiology will be able to meet the public's demands for service in the years ahead? To answer this question, it is necessary to examine the trends in demand in each of radiology's principal divisions. In diagnostic roentgenology, clinical demand is reflected in statistics on the number of examinations performed. A few years ago, the U. S. Public Health Service published examination data for the year 1964. The Service is currently collecting similar data for 1970. Although, the results of the latest study will not be available until next year, preliminary figures indicate that the number of x-ray procedures performed annually in the United States is growing at a rate in excess of 5%.

It has been previously pointed out by NACOR that the growth in the number of x-ray examinations performed provides only a partial indication of the increase in the service demand in diagnostic roentgenology. Because of technological developments during the past two decades, a series of new radiological procedures of fundamental importance to the diagnosis of many disease states has been introduced. Among these may be included examinations of the cardiac, pulmonary, cerebral, renal, portal and peripheral circulations as well as procedures to delineate abnormal physiology within the gastrointestinal, respiratory and genitourinary systems. One of the important characteristics of these new methods is

TABLE III

DISTRIBUTION OF PROFESSIONAL MANPOWER
ARRANGED ACCORDING TO RADIOLOGICAL
DISCIPLINE IN 17 UNIVERSITY HOSPITALS<sup>9</sup>

Discipline	Per cent	
Diagnostic Roentgenology	72	
Radiation Therapy	16	
Nuclear Medicine	12	
Total	100	

that they need much more time and effort for their performance than do older more conventional techniques. Although these procedures account for only a small fraction of all examinations undertaken in the United States, they require a substantial portion of the professional manpower available in diagnostic roentgenology for their performance. Because of this, it has been estimated by NACOR that the demand for diagnostic radiological services, measured in terms of the load imposed upon the radiological manpower pool, is growing at a rate at least one third greater than that indicated by data on the number of examinations performed. That is, it appears that the clinical demand for diagnostic radiological services is growing at an annual rate of approximately 6.7%.

Support for this estimate may be gained from an examination of Figure 2, charting the consumption of medical x-ray film within the United States over the past 20 or more years. It will be observed that during this time, consumption increased at an average annual compounded rate of almost 6.8% and that currently this rate exceeds 10%. There can be little question that demands upon the manpower pool in diagnostic roentgenology are growing at least as rapidly as the pool itself and almost certainly much faster.

In radiation therapy, demand for clinical services is growing less rapidly. Here, demand is related to the frequency of occurrence of cancer which in recent years has been rising at an annual rate of about 2%. However, because of the increasing proportion of cancer patients found suitable for radiation treatment, service demands in this field appear to be increasing somewhat faster, perhaps at an annual rate approaching 3%.

In nuclear medicine, growth patterns are difficult to evaluate. Demands for clinical service have risen in the brief span of a few years to a level requiring more than one tenth of the professional manpower devoted to clinical radiology. These data together with hospital statistics from a number of

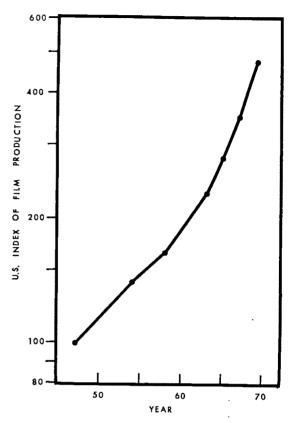


Fig. 2. Index of consumption of medical x-ray film in the United States.

institutions where patient records in nuclear medicine have been maintained for an adequate period of time suggest that this discipline's growth rate is at least 15% per year and may actually be higher.

Taken together, the growth rate in the demand for clinical services in diagnostic roentgenology, radiation therapy and nuclear medicine, weighed in accordance with the data presented in Table III, currently is in excess of 7% per year. Furthermore, this pattern has followed a course which clearly indicates that it is likely to be maintained in the future.

Parenthetically, it is noteworthy that although radiology has enjoyed a sustained growth in professional manpower over a protracted period of time, its numbers are still relatively small when expressed in terms of the total pool of practicing physicians (Table IV). Also, several other specialties have shown manpower growth rates

Table IV

NUMBER OF PHYSICIANS, EXCLUSIVE OF INTERNS AND RESIDENTS IN TRAINING IN THE UNITED STATES ON DECEMBER 31, 19678

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Type of Practice	Number of Physicians	Per cent of Total	
General Practice	68,207	26.2	
Internal Medicine	34,270	13.1	
General Surgery	22,698	8.7	
Psychiatry	16,124	6.2	
Obstetrics-Gynecology	15,297	5.8	
Pediatrics	14,116	5.4	
Radiology	8,734	3.3	
Anesthesiology	8,334	3.2	
Ophthalmology	7,836	3.0	
Pathology	7,250	2.7	
Orthopedic Surgery	6,869	2.6	
Others	52,039	19.8	
Total Active Physicians	261 ,774	1∞.0	

comparable to those experienced by radiology (Table v). However, as we shall see presently, there has recently been a marked change in specialty preference, particularly favorable to radiology, among medical graduates. Hence, these relationships are likely to be altered substantially in the years ahead.

The disparity between the growth in the public's demand for radiological services (7%) and the growth in radiological manpower to meet this demand (5.7%) presents a problem of some magnitude. How can the gap be closed? Each year that it is allowed to exist, the supply-demand equation becomes increasingly out of balance, the cost of radiological services escalates and the clinical burden becomes greater. The solution to this problem constitutes one of the great challenges facing radiology today.

A number of solutions have been proposed. Knowles<sup>5</sup> has suggested that specialists who refer cases for radiological study increasingly undertake responsibility for reporting these cases for the clinical record. He points out that many of these physicians are quite competent to perform this task in their particular fields of specialization. This

solution, however, has certain inherent dangers, not the least of which is the possibility that disease processes outside of the specialist's field of interest will be overlooked. Another difficulty pertains to the time which various specialists have available for such tasks as radiological reporting. In my experience, many of these men have precious little time for this responsibility; indeed, they have difficulty in maintaining the clinical records for which they are primarily responsible. This solution can provide only a very small answer to the radiology manpower problem.

Other solutions that have been suggested include:

- 1. the training of more radiologists;
- 2. the creation of a new manpower pool composed of radiological assistants capable of relieving the professional radiologist of certain portions of his clinical burden;
- 3. the development of new techniques increasing the efficiency with which the tasks of radiologists are carried out; and
- 4. the careful review of the demand for radiological services with the objective of eliminating that portion of the demand not supported by sound clinical indication.

Table V

ANNUAL GROWTH RATES OF PROFESSIONAL MANPOWER, ARRANGED ACCORDING TO SPECIALTY
FOR PERIOD 1963-1967

Specialty	Growth Rate (per cent)
Pathology	6.5
Anesthesiology	5.8
Radiology	5.7
Pediatrics	5.4
Orthopedic Surgery	5.3
Psychiatry	5.2
Internal Medicine	5.0
General Surgery	3.8
Ophthalmology	3.6
Obstetrics-Gynecology	3.3

# IV. THE TRAINING OF ADDITIONAL RADIOLOGICAL MANPOWER

In 1965, when NACOR examined the manpower problem in radiology, it appeared that there was little hope that even a partial solution might be achieved from efforts to increase the number of clinical radiologists. The number of residents in training had remained relatively constant over the preceding decade. Over one quarter of the residency positions available were unfilled. Academic radiology appeared ill-equipped to undertake a task which would impose upon it a substantial increase in the training load. Radiological faculties were finding it increasingly difficult to keep up with the burgeoning service demands, characteristic of all university hospitals. Less and less time was available for teaching it seemed and little or no effort could be directed to the sort of exciting research programs needed to attract increasing numbers of students into radiology.

A few years earlier, the specialty of psychiatry when faced with manpower problems similar to those prevailing in radiology, had persuaded Congress and the National Institutes of Health to establish a crash program for the training of additional psychiatrists. Substantial amounts of money were provided to increase the training capability of academic departments of psychiatry and to attract additional trainees to the specialty. The program had been reasonably successful and it was thought wise to adapt it to clinical radiology. However, funds from governmental sources for training were becoming more difficult to obtain and although the National Institute of General Medical Sciences undertook a program designed to train additional academic radiologists, no effort was instituted to find a solution to the radiological manpower problem generally.

In spite of its burdens and difficulties, academic radiology in 1965 went quietly to work to train increasing numbers of diagnostic roentgenologists, radiation therapists and specialists in the field of nuclear medicine. Using the limited resources available and with little outside help, it took the steps needed to attract medical students to radiology early in their careers and to provide interesting training opportunities for these individuals during their residency programs. What has happened during the past five years is a magnificent example of what can be done when a group of individuals makes up its mind to achieve a worthy objective. I do not wish to imply that academic radiology carefully planned its course of action and then assiduously carried it out. On the contrary, the effort had little or no organization and yet the driving spirit, consciously or unconsciously, was always pres-

In May of 1965, the Association of University Radiologists, meeting in Seattle, expressed considerable concern for the growing shortage of radiologists, particularly in academic training centers. As reported by Abrams,1 the topic was dictated by urgency rather than by preference and was discussed at great length. It was concluded that if the number of individuals seeking radiological training after graduation from medical school were to be significantly increased, the instruction of these students in the radiation sciences in the undergraduate years had to be markedly improved. Quantitative as well as qualitative changes were needed. Increased opportunities for the student to learn the role of radiology in modern medicine had to be provided.

It was idle to expect major changes in curriculum to accommodate the objectives that academic radiology had in mind. Hence, alternative ways of gaining contact with the student were undertaken. Academic radiologists in increasing numbers began participating in the instruction of students during the anatomy, physiology and pathology courses. Advantage was taken of the increased allotment of free time in many medical schools to establish radiological electives which would be stim-

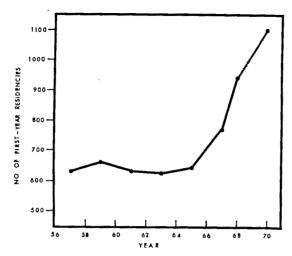


Fig. 3. Number of first year residencies offered in radiology.

ulating as well as instructive to the students who wished to take them.

The results of this effort are shown dramatically in Figure 3 where the number of first year residencies available in radiology are plotted against time. As previously pointed out, the number had remained relatively constant for the decade prior to 1965. Then suddenly, the number increased from the low 600s to the mid 900s in 1968. More recent data are not available but projections of recent trends suggest that the number of first year residencies is now close to the 1,100 level. Of equal sig-

nificance is the increase in the proportion of first-year residencies which are now filled. This percentage has risen sharply from approximately 70% in 1955 to 90% in 1968. Moreover, these residencies are flled with a higher proportion of graduates from American medical schools than almost any other discipline (Table vi). Surely, in the minds of American medical students, radiology has emerged as one of the major disciplines of clinical medicine. Of all of the clinical specialties, it stands fourth in its attraction to medical students on an absolute basis and first on a relative basis (Table VII). It is noteworthy that these changes have been accompanied by substantial increases in the number of applicants for the residency positions available. At Johns Hopkins University, it used to be considered a good year when 50 applications were received for the 4 or 5 openings available. Now, the number of applicants has reached almost 200 each year. Other academic institutions have had a similar experience. With the increase in applicants, their quality has improved as well.

Although such a question would have seemed quite inappropriate just a few years ago, it may now be reasonably asked if the effort to train more radiologists is not becoming too successful. Can American medicine afford to have almost 10% of its gradu-

Table VI

FIRST YEAR RESIDENCIES OFFERED IN VARIOUS SPECIALTIES ON SEPTEMBER 1, 19688

Specialty	No. of Positions	No. Filled	Per cent Filled	No. Filled by U.S. Graduates	Per cent Filled by U.S. Graduates
Anesthesiology	846	677	80	349	52
Internal Medicine	2,885	2,589	90	1,801	70
Neurology	293	249	85	190	, 76
Obstetrics-Gynecology	879	759	86	433	57
Ophthalmology	431	418	97	386	93
Pathology	1,100	661	60	302	42
Pediatrics	1,161	1,002	86	596	60
Psychiatry	1,657	1,200	73	828	69
Radiology	941	849	90	687	81
General Surgery	2,718	2,394	88	1,580	67
All Specialties	15,365	12,721	83	8,573	$\dot{67}$

ating students enter radiology? What problems will this create in such other important disciplines as pediatrics, obstetrics and gynecology, and pathology where the percentages are substantially smaller? Although its consequences in these other specialties should not be minimized, I firmly believe that American medicine not only can but must afford this level of radiological specialization if more serious problems are to be avoided in the years ahead.

It is noteworthy that even at the 10% level, the number of new graduates who take their training in radiology will not meet the manpower needs of this specialty. Such a percentage represents about 800 new trainees each year. However, approximately 200 radiologists retire annually and hence, the net gain in manpower is only 600, or about 6.5% of the manpower pool. Such an increase, as we have seen, is less than the rate of growth in the demand for radiological services.

Manpower problems in medicine generally may be expected to be relieved somewhat over the next decade by the opening of a number of new medical schools and by increases in the student bodies of schools now in existence. The number of students graduating each year will likely increase about 30% by 1980 and more thereafter. This will help those specialties whose growth rates are relatively modest; however, it will have little influence on radiology whose manpower needs are rising so rapidly. That is, increases in the manpower supply of 30% spread over 10 years will be of little help to a specialty whose requirements are increasing 7% annually. One can only conclude from this that, although academic radiology has accomplished a great deal in its efforts to fulfill the manpower needs of the specialty, the numbers of graduating medical students, now and in the foreseeable future, are simply not enough to meet radiology's needs without seriously disturbing the manpower balance among other medical specialties.

Before leaving the subject of physician training in radiology, I should like to call

TABLE VII

number of first year residents, graduated from american medical schools, for each 1,000 practicing physicians in various fields of specialization on september 1, 1968

Specialty	No. of Resident				
Radiology	79				
General Surgery	70				
Internal Medicine	53				
Psychiatry	51				
Ophthalmology	49				
Anesthesiology	42				
Pediatrics	42				
Pathology	41				
Obstetrics-Gynecology	28				

attention to a special problem that has arisen in radiation therapy. At the present time, approximately 800,000 new cases of cancer develop each year in the United States, and of these a little more than half, or about 450,000, are suitable for treatment by ionizing radiation. Now it is generally believed that a full-time radiation therapist can take care of 300 new cancer patients each year. Hence, about 1,500 of these specialists are needed in the nation as a whole. (Note that this represents about 15% of the total radiological manpower pool and corresponds closely to the estimates made by NACOR in Table III.)

In the past, most of the radiation therapy in the United States has been performed by radiologists who have also practiced as diagnostic roentgenologists. However, as the separation of the radiological disciplines has become more complete, the work in radiation therapy has fallen increasingly on the full-time specialists. Since there are only about 600 of these, it is clear that more are needed. Unfortunately, radiation therapy has had some difficulty in recruiting trainees. About 15% of the resident pool or close to 400 residents should now be in training in the specialty but only about half that number can be identified. As a solution to this problem, I should like to suggest that radiation therapy strengthen its relationships with internal medicine in

our medical schools. By participating in medical student teaching in internal medicine, radiation therapy can establish the pathways needed to attract recruits who have a strong interest in patient care, an interest so necessary for the handling of cancer patients, and an interest often found wanting among trainees entering other radiologic disciplines. The advent of chemotherapeutic methods in cancer has caused internal medicine to become increasingly concerned for patients with neoplastic disease and a close association between the two disciplines seems to offer great opportunity for mutual benefit.

# V. DO RADIOLOGICAL ASSISTANTS PROVIDE AN ANSWER TO THE RADIOLOGICAL MANPOWER PROBLEM?

Because it appears unlikely that manpower needs in radiology will be met in the years ahead, it has been suggested by some that we begin to train a class of individuals, educated to a level less than that of physicians, who are able to perform many of the functions now carried out by radiologists. Specifically, it has been proposed that radiological technologists, after a period of further training, be allowed to undertake such tasks as fluoroscopy and the interpretation and reporting of some x-ray examinations under the supervision of radiologists. I worry about a proposal of this sort. I doubt that the educational background of most technologists today is adequate to allow them to relieve radiologists of any substantial amount of their professional duties without a great deal more training.

However, the idea of using individuals, trained below the level of the M.D. degree, to share some of the burdens of radiologists is an intriguing one if the proper educational formula can be found. As one possible step in this direction, I would like to see an experimental program established in a few centers in which individuals enter a 4 year baccalaureate program with emphasis on biology, physics and chemistry during the

first 2 years and on anatomy, physiology, pathology and radiology in the last 2 years. Upon graduation, the student might receive a Bachelor of Medical Science degree and then go on to a year of radiological internship in a well supervised department of radiology.

Individuals who have taken such training should be able to assume a great deal of professional responsibility under the direction of a radiologist. Because they would be 5 years beyond high school when they complete their training, they might also be expected to have the maturity which their responsibilities require. On the other hand, they would assume these responsibilities at an age 8 years earlier than radiologists who currently spend 13 years beyond high school before they become eligible for certification by the American Board of Radiology.

I am not advocating that a bachelor of medical science program for radiological assistants be undertaken on a wide scale until it has been proved effective in a number of centers under experimental conditions. However, if it is successful, the program may be very useful in helping to meet some of the radiological manpower shortages that seem so certain to lie ahead.

The use of radiological assistants as professionals, of course, will pose a number of problems. Educational and licensing standards must be carefully worked out. The extent of clinical responsibility must be clearly established. One of the most difficult problems concerns the determination of competence. If radiological assistants are to assume substantial responsibility heretofore borne only by the radiologist, one must be certain that their assignments can be effectively carried out. One of the fears in the minds of many is that training programs for radiological assistants will not be adequate to qualify graduating students for the work they will be called upon to perform. How can this problem be avoided? Clearly, it calls for the development of qualifying examinations which have been prepared with considerable care.

The preparation of such examinations fortunately has been greatly facilitated in recent years by advances in our understanding of the processes of medical decision making. By the use of concepts developed in signal detectability theory, recently reviewed by Lusted, it is now possible to devise tests which not only permit the examiner to gain a qualitative opinion of the examinee but a quantitative impression as well.

To illustrate this, let us consider the case where one wishes to examine a candidate's competence to detect from conventional. roentgenograms of the chest the presence of pulmonary disease. If one collects a series of 100 or more films, a certain number of which exhibit disease in various stages of development and the remainder are negative, and if this group of films is submitted to the candidate to be examined, his interpretations will fall into 4 categories. Of the positive cases, some will be properly interpreted as showing disease (true positives). However, some will be misinterpreted as exhibiting no pathology (false negatives). Similarly, of the normal films, some will be correctly called negative (true negatives), while some will be interpreted as showing disease even though none is present (false positives).

Now if the candidate is highly competent, he may be expected to interpret a very large proportion of the positive cases as showing disease and a large proportion of the negative cases as being normal. On the other hand if the candidate has little competence, his performance will be quite erratic with a very low correlation between his interpretations and what the films actually convey.

The level of an individual's competence can be evaluated from a test of the sort just described by applying the candidate's scores in the true positive and false positive categories to a set of so-called receiver operating characteristic (ROC) curves (Fig. 4). If the candidate's experience is such that he has little understanding of the task to be performed his performance will fall

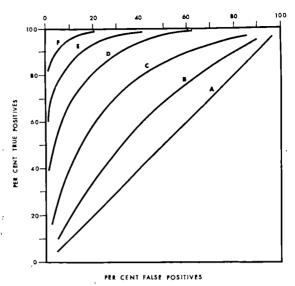


Fig. 4. Typical curves of reader performance (socalled receiver operating characteristic curves). Curve A illustrates the line along which the performance data of a group of individuals having little or no competence to perform the assigned reading tasks may be expected to fall. Curves B through F indicate the loci of the performance data of individuals of increasing competence.

close to the diagonal line (curve A). On the other hand if he has had a little training and hence has developed some competence, his interpretations will include a greater proportion of true positives and a smaller proportion of false positives so that his performance might then fall at some position along curve B. As more and more training is provided and as his competence becomes still greater, ultimately, a performance level is reached corresponding to that of a well-trained radiologist where almost all of the true positives are detected and very few errors of the false positive variety are made; that is, the performance may be such as to lie somewhere along curve F.

In any particular situation, the curve applicable to a highly qualified reader will depend upon a number of factors including the nature and state of the disease processes to be detected. For example, in the case of minimal tuberculosis where the lesions are small and difficult to see, even a well-trained radiologist may exhibit a

relatively large number of errors in both negative and positive categories. Under this circumstance, his performance might fall at some position along curve D. On the other hand, in other disease states, where the manifestations of disease are easily seen, errors will be small and the performance of a qualified reader might fall at some position along curve F.

It is evident from Figure 4 that examination techniques may be devised whereby the candidate's ability to detect disease from x-ray films can be measured quantitatively and compared with that of qualified readers. The means are therefore available by which the qualifications of radiological assistants can be tested. Furthermore, if one wishes, one can extend these techniques to measure a candidate's ability not only to detect disease but to classify it according to its underlying pathology. Alcorn and O'Donnell' have used these techniques to evaluate the performance of six individuals who were trained as radiological assistants to screen mammograms for breast carcinoma. The results of this study indicate that these nonprofessionals developed considerable skill in the separation of cases positive for breast carcinoma from those which were negative. A plot of their true positive-false positive data fell approximately along the locus of curve C. Although this performance is not as good as that shown by qualified radiologists, it nevertheless was fairly respectable and indicated that with additional training, the competence of these individuals might reach a high level.

Although the case for radiological assistants is still to be proven, there is evidence to indicate that means are available to evaluate them thoroughly before responsibilities are assigned to them.

### VI. INCREASING THE EFFECTIVENESS OF AVAILABLE RADIOLOGICAL MANPOWER

In spite of all of the effort that can be reasonably marshalled to increase the number of radiologists and radiological assistants, there is still reason to believe that manpower requirements will continue to fall substantially short of clinical demand. The question must therefore be asked what can be done to better utilize the manpower available to us. There are no easy answers to this question. However, it is so important that practical solutions be found that it is incumbent on every one of us to give the most serious attention to the development of ways and means by which the radiological services for which we are responsible may be delivered more efficiently. Better methods of patient scheduling and management, more efficient techniques of film filing and retrieval, and improved ways of getting radiological information to the patient's physician must be devised. In these developments, the concepts of systems engineering should be applied wherever possible.

Any discussion of methods to improve radiological practice requires that careful attention be given to the over-all system by which medical care is delivered in the United States. This system, which has been characterized as a "non-system" with uneven quality and distribution of services, wasteful application of resources and inequitable financing,10 has come under severe criticism in recent years. It has been alleged that medical and surgical services are lavishly bestowed on certain classes of patients, often with little clinical benefit, while at the same time other patients are neglected or unable to obtain the services they need and desire. Unfortunately, these allegations are, at least to some degree, true; the system of health care in the United States currently leaves a great deal to be desired. Why has this situation been allowed to develop? There are many reasons but one unquestionably is the rapid growth of medical science during the past three or four decades. Changes have occurred so quickly that there have been few opportunities to optimize patterns of health care as new procedures have become available. It is also unfortunate that the usual market forces of choice, price and measurable perating students enter radiology? What problems will this create in such other important disciplines as pediatrics, obstetrics and gynecology, and pathology where the percentages are substantially smaller? Although its consequences in these other specialties should not be minimized, I firmly believe that American medicine not only can but must afford this level of radiological specialization if more serious problems are to be avoided in the years ahead.

It is noteworthy that even at the 10% level, the number of new graduates who take their training in radiology will not meet the manpower needs of this specialty. Such a percentage represents about 800 new trainees each year. However, approximately 200 radiologists retire annually and hence, the net gain in manpower is only 600, or about 6.5% of the manpower pool. Such an increase, as we have seen, is less than the rate of growth in the demand for radiological services.

Manpower problems in medicine generally may be expected to be relieved somewhat over the next decade by the opening of a number of new medical schools and by increases in the student bodies of schools now in existence. The number of students graduating each year will likely increase about 30% by 1980 and more thereafter. This will help those specialties whose growth rates are relatively modest; however, it will have little influence on radiology whose manpower needs are rising so rapidly. That is, increases in the manpower supply of 30% spread over 10 years will be of little help to a specialty whose requirements are increasing 7% annually. One can only conclude from this that, although academic radiology has accomplished a great deal in its efforts to fulfill the manpower needs of the specialty, the numbers of graduating medical students, now and in the foreseeable future, are simply not enough to meet radiology's needs without seriously disturbing the manpower balance among other medical specialties.

Before leaving the subject of physician training in radiology, I should like to call

TABLE VII

NUMBER OF FIRST YEAR RESIDENTS, GRADUATED FROM AMERICAN MEDICAL SCHOOLS, FOR EACH 1,000 PRACTICING PHYSICIANS IN VARIOUS FIELDS OF SPECIALIZATION ON SEPTEMBER 1, 19688

Specialty	No. of Residents
Radiology	79
General Surgery	70
Internal Medicine	53
Psychiatry	51
Ophthalmology	49
Anesthesiology	42
Pediatrics	42
Pathology	4.I
Obstetrics-Gynecology	28

attention to a special problem that has arisen in radiation therapy. At the present time, approximately 800,000 new cases of cancer develop each year in the United States, and of these a little more than half, or about 450,000, are suitable for treatment by ionizing radiation. Now it is generally believed that a full-time radiation therapist can take care of 300 new cancer patients each year. Hence, about 1,500 of these specialists are needed in the nation as a whole. (Note that this represents about 15% of the total radiological manpower pool and corresponds closely to the estimates made by NACOR in Table III.)

In the past, most of the radiation therapy in the United States has been performed by radiologists who have also practiced as diagnostic roentgenologists. However, as the separation of the radiological disciplines has become more complete, the work in radiation therapy has fallen increasingly on the full-time specialists. Since there are only about 600 of these,11 it is clear that more are needed. Unfortunately, radiation therapy has had some difficulty in recruiting trainees. About 15% of the resident pool or close to 400 residents should now be in training in the specialty but only about half that number can be identified. As a solution to this problem, I should like to suggest that radiation therapy strengthen its relationships with internal medicine in

our medical schools. By participating in medical student teaching in internal medicine, radiation therapy can establish the pathways needed to attract recruits who have a strong interest in patient care, an interest so necessary for the handling of cancer patients, and an interest often found wanting among trainees entering other radiologic disciplines. The advent of chemotherapeutic methods in cancer has caused internal medicine to become increasingly concerned for patients with neoplastic disease and a close association between the two disciplines seems to offer great opportunity for mutual benefit.

## V. DO RADIOLOGICAL ASSISTANTS PROVIDE AN ANSWER TO THE RADIOLOGICAL MANPOWER PROBLEM?

Because it appears unlikely that manpower needs in radiology will be met in the years ahead, it has been suggested by some that we begin to train a class of individuals, educated to a level less than that of physicians, who are able to perform many of the functions now carried out by radiologists. Specifically, it has been proposed that radiological technologists, after a period of further training, be allowed to undertake such tasks as fluoroscopy and the interpretation and reporting of some x-ray examinations under the supervision of radiologists. I worry about a proposal of this sort. I doubt that the educational background of most technologists today is adequate to allow them to relieve radiologists of any substantial amount of their professional duties without a great deal more training.

However, the idea of using individuals, trained below the level of the M.D. degree, to share some of the burdens of radiologists is an intriguing one if the proper educational formula can be found. As one possible step in this direction, I would like to see an experimental program established in a few centers in which individuals enter a 4 year baccalaureate program with emphasis on biology, physics and chemistry during the

first 2 years and on anatomy, physiology, pathology and radiology in the last 2 years. Upon graduation, the student might receive a Bachelor of Medical Science degree and then go on to a year of radiological internship in a well supervised department of radiology.

Individuals who have taken such training should be able to assume a great deal of professional responsibility under the direction of a radiologist. Because they would be 5 years beyond high school when they complete their training, they might also be expected to have the maturity which their responsibilities require. On the other hand, they would assume these responsibilities at an age 8 years earlier than radiologists who currently spend 13 years beyond high school before they become eligible for certification by the American Board of Radiology.

I am not advocating that a bachelor of medical science program for radiological assistants be undertaken on a wide scale until it has been proved effective in a number of centers under experimental conditions. However, if it is successful, the program may be very useful in helping to meet some of the radiological manpower shortages that seem so certain to lie ahead.

The use of radiological assistants as professionals, of course, will pose a number of problems. Educational and licensing standards must be carefully worked out. The extent of clinical responsibility must be clearly established. One of the most difficult problems concerns the determination of competence. If radiological assistants are to assume substantial responsibility heretofore borne only by the radiologist, one must be certain that their assignments can be effectively carried out. One of the fears in the minds of many is that training programs for radiological assistants will not be adequate to qualify graduating students for the work they will be called upon to perform. How can this problem be avoided? Clearly, it calls for the development of qualifying examinations which have been prepared with considerable care.

The preparation of such examinations fortunately has been greatly facilitated in recent years by advances in our understanding of the processes of medical decision making. By the use of concepts developed in signal detectability theory, recently reviewed by Lusted, it is now possible to devise tests which not only permit the examiner to gain a qualitative opinion of the examinee but a quantitative impression as well.

To illustrate this, let us consider the case where one wishes to examine a candidate's competence to detect from conventional

roentgenograms of the chest the presence of pulmonary disease. If one collects a series of 100 or more films, a certain number of which exhibit disease in various stages of development and the remainder are negative, and if this group of films is submitted to the candidate to be examined,

his interpretations will fall into 4 categories. Of the positive cases, some will be properly interpreted as showing disease (true positives). However, some will be misinterpreted as exhibiting no pathology

(false negatives). Similarly, of the normal films, some will be correctly called negative (true negatives), while some will be interpreted as showing disease even though none

is present (false positives).

Now if the candidate is highly competent, he may be expected to interpret a very large proportion of the positive cases as showing disease and a large proportion of the negative cases as being normal. On the other hand if the candidate has little competence, his performance will be quite erratic with a very low correlation between his interpretations and what the films actually convey.

The level of an individual's competence can be evaluated from a test of the sort just described by applying the candidate's scores in the true positive and false positive categories to a set of so-called receiver operating characteristic (ROC) curves (Fig. 4). If the candidate's experience is such that he has little understanding of the task to be performed his performance will fall

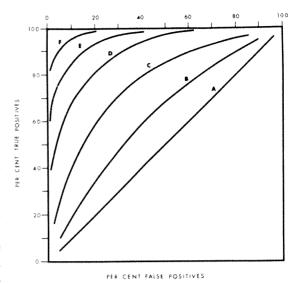


Fig. 4. Typical curves of reader performance (socalled receiver operating characteristic curves). Curve A illustrates the line along which the performance data of a group of individuals having little or no competence to perform the assigned reading tasks may be expected to fall. Curves B through F indicate the loci of the performance data of individuals of increasing competence.

close to the diagonal line (curve A). On the other hand if he has had a little training and hence has developed some competence, his interpretations will include a greater proportion of true positives and a smaller proportion of false positives so that his performance might then fall at some position along curve B. As more and more training is provided and as his competence becomes still greater, ultimately, a performance level is reached corresponding to that of a well-trained radiologist where almost all of the true positives are detected and very few errors of the false positive variety are made; that is, the performance may be such as to lie somewhere along curve F.

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Any discussion of methods to improve radiological practice requires that careful attention be given to the over-all system by which medical care is delivered in the United States. This system, which has been characterized as a "non-system" with uneven quality and distribution of services, wasteful application of resources and inequitable financing, 10 has come under severe criticism in recent years. It has been alleged that medical and surgical services are lavishly bestowed on certain classes of patients, often with little clinical benefit, while at the same time other patients are neglected or unable to obtain the services they need and desire. Unfortunately, these allegations are, at least to some degree, true; the system of health care in the United States currently leaves a great deal to be desired. Why has this situation been allowed to develop? There are many reasons but one unquestionably is the rapid growth of medical science during the past three or four decades. Changes have occurred so quickly that there have been few opportunities to optimize patterns of health care as new procedures have become available. It is also unfortunate that the usual market forces of choice, price and measurable perBase.

formance, by which consumers are able to control generally the kind of services they receive, do not apply in medicine. Patients often do not have available to them the information required to select their medical care wisely and rationally. Instead, the selection process is usually haphazard with the control of the medical services rendered essentially in the hand of the physician chosen. As a consequence, the usual checks and balances of the market place have not operated to maintain an even flow of medical services, carefully optimized in terms of benefit and cost, under the rapidly changing conditions associated with the expansion in medical knowledge.

In view of the foregoing, it is not surprising that the health care system has encountered severe strains and dislocations; it is not surprising that costs of medical care have risen precipitously; and it is not surprising that the consuming public has become discontented.

VII. THE DEMAND FOR RADIOLOGICAL SERVICES: CAN IT BE REDUCED BY JUDICIOUS SELECTION OF CASE MATERIAL

Although radiology until recently has constituted only a relatively small part of the health care system, its emergence as a major medical discipline requires that it play a significant role in improving this system in the years ahead. In many respects, the quality and distribution of radiological services in the United States are as uneven as those of medical services generally; furthermore, the rapidly increasing number of elaborately equipped facilities, often used for only limited periods of each day, must raise serious questions concerning the effectiveness with which we are utilizing our resources. Have we become as wasteful in the application of these resources as our critics claim?

Even more serious than the foregoing is the growing tendency of the medical profession to use radiological methods for purposes other than to answer clinical questions for which these methods are uniquely suited. I am speaking here of the increasing extent to which our services are used without careful consideration of clinical benefit and cost, without thorough clinical evaluation of the patient, and often as a means merely to provide medico-legal protection. In a recent study of the information yield of skull films in head trauma, Bell and Loop<sup>3</sup> have shown that certain specific clinical indications when applied prior to the routine radiography of the skull might have reduced by one third the number of radiological procedures undertaken without the oversight of any fractures. Moreover, among the patients with fracture, only 30% had their course of therapy altered by the finding of fracture. Even in these cases, the benefits of radiological examination were uncertain because many patients die or are permanently disabled whatever the treatment. Bell and Loop estimated that 50 million dollars are spent each year on radiological examinations of the skull to discover only a tiny number of head trauma victims whose prognosis will be significantly improved thereby.

The foregoing illustration clearly indicates the urgent need for studies by which the clinical benefits of radiological procedures are critically evaluated and the conditions under which these procedures are applied are carefully optimized. The system of medical care in the United States has tended to avoid investigations of this sort, investigations which measure quality of performance and which suggest alternative means which potentially yield greater information at lower cost. However, such studies are essential to the improvement of the health care system and to the solution of the radiological manpower problem. If unnecessary radiological services were eliminated by any fraction, our manpower problems would be correspondingly alleviated. Our manpower resources are not unlimited. Mechanisms must be found which will concentrate the use of diagnostic and therapeutic procedures among those patients for whom the expectation of benefit is clearly evident. To achieve this objective will require long and painstaking work. This, however, is no more than should be expected of a specialty that has now achieved major status among the principal medical disciplines.

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### A COMPARATIVE STUDY OF RADIOLOGIST'S TIME UTILIZATION IN VARIOUS REPORTING SYSTEMS\*

By JOHN R. THORNBURY, M.D. ANN ARBOR, MICHIGAN

THE chronic shortage of radiologists to perform the diagnostic radiology that clinical workloads require is painfully obvious in daily practice. One means of at least partially alleviating this situation is to find ways of making more efficient use of the radiologist's time in performing his clinical tasks.

This paper is a preliminary report of experimental evaluation of one aspect of the radiologist's workload–radiologic reporting systems.

The investigation reveals that much less time is required for the radiologist to interpret and report plain film roentgenographic examinations if he dictates in a computer style term format rather than traditional prose descriptive, sentence style. His time is further more efficiently used if current and comparable old roentgenograms are previously selected and displayed on an automated viewing device by a clerk.

In 1969 at the University of Michigan Hospital we began to study reporting systems as part of an evaluation of the possibility of going to a computer oriented total patient data base. Four types of reporting systems were investigated by film reading dictation experiments carried out by I staff radiologist and 2 residents (I second, I third year). The 4 reporting systems evaluated were: (I) nonassisted prose format; (2) clerk assisted prose format; (3) nonassisted computer format; and (4) clerk assisted computer format.

Prose dictation (Report 1) has been the traditional reporting method used since radiology began. The amount of information in this descriptive method using sentence structure varies greatly from individual to individual. Brevity is related to expediency

as well as personal preference as to the amount of detail needed to support one's conclusions and confidence. Commonly, the less confident the diagnosis, the longer and more vague the prose report.

The computer type format report (Report II) represents a restricted information system using terms rather than sentences. This requires more stringent information organization by the radiologist before input into the recording system, be it computer or dictating device. We were interested in seeing how comfortable, as well as how efficient, radiologists would be in using this unfamiliar system.

Clerk assistance in film sorting and display for reading has been used in some departments. It is certainly less distracting for a radiologist not to have to shuffle through a large jacket of films, but our main interest was in determining just how much time clerk assistance saves the radiologist compared to the non-clerk assisted, "pare down the stack" approach.

### EXPERIMENTAL DESIGN

All the film reading dictation experiments were done in an 8×10 foot reading room in the Urological Radiology Suite in our department. The automated viewing device used was a 50 frame, 200 film capacity, S and S unit. An IBM magnetic belt dictating machine was used for information recording. Film data were comprised of 2 groups of 12 cases each, which included excretory urogram, chest, and metastatic bone survey examinations. No fluoroscopic studies were involved.

Report content was made as comparable as possible by including the following items in either computer or prose format:

From the Department of Radiology, University Hospital, Ann Arbor, Michigan.

<sup>\*</sup> Presented at the Seventy-first Annual Meeting of the American Roentgen Ray Society, Miami Beach, Florida, September 29-October 2, 1970.

- (1) Patient's name and hospital number
- (2) Type of examination
- (3) Roentgenologic findings
- (4) Comparison with previous examination (when appropriate) and recommended additional studies
- (5) Roentgenologic diagnosis (including differential diagnosis where indicated)
- (6) Diagnostic code.

Ground rules for the unfamiliar computer format were written down, and each radiologist familiarized himself with these before the experiment. Basically, the idea was to record the pertinent observations in noun form with the most limited modifiers, and list these findings in numerical order. Normal findings were recorded only when pertinent. The only other requirement was that the radiologist make it a point to answer the question posed by the referring physician on the consultation request.

The systems were compared on the basis of the total time required for radiologist's interpretation and reporting in the various systems. The 2 basic variables in the experimental studies were: (1) the type of information organization (prose vs. computer format); and (2) clerk assistance in preselecting current and comparable examinations for display of films on an automated viewing device.

The first part of the experiment compared computer vs. prose format using clerk assistance in both systems. A clerk preselected the current and most recent comparable films of all 12 cases and mounted them on the automated viewing device. The folder of previous reports was clipped to the front of each master film jacket, and the jackets were at hand on the viewing device table top for reference if needed.

The radiologist was isolated with the displayed films in the reading room, and without interruption reported Group I of 12 cases in computer format. Then he repeated the reporting of the same 12 cases but used prose format. On a subsequent day, the radiologist reported Group II of 12 different

cases but this time reversed dictation order using prose first and then computer format second for the repeat reading. This reversal of format order was done to offset the bias favoring second reading due to familiarity with the roentgenologic findings on the initial reporting sequence. Time was determined for each system from the start of looking at Case 1 to the end of dictation of Case 12.

The second part of the experiment demonstrated the effect of clerk assistance on either the computer or prose format system. The radiologist reported 1 of the groups of 12 cases without clerk assistance in one of the two formats. The films were presented to him as a pile of 12 master film jackets placed on the viewing device table top. The current films and consultation requests were clipped to the front of each master jacket. The folder of old reports and all previous films were inside the master jacket. The two visible frames on the viewing device (equivalent to eight 14×17 inch films, "four-on-four") were the only ones used. The radiologist put up the films, "read them out," took them down, replaced them in the jacket, and went on to the next case without interruption. Again, total time was from the start of looking at Case 1 to the end of dictation of Case 12. Times for this non-assisted method were compared with the clerk assisted studies done by the same radiologist using the same cases 8 months previously.

### RESULTS

Details of the dictating time comparisons for formats are shown in Table 1. The bias favoring repeat reading of the same material is present, regardless of whether computer or prose format was used first. However, the time of the repeat reading was much less with computer format than with prose format. For each radiologist the computer format was at least twice as effective as prose format in reducing the repeat reading time.

The computer format provided additional time saving by decreasing the time

TABLE I

COMPARISON OF READING TIME FOR PROSE

05. COMPUTER FORMAT

Case Group		Radiologist	T (min.)	Format		
Α.	Com	puter Forma	t First			
	1	Staff	33	100	Computer	
			31	94	Prose	
	I	Resident 2	46	100	Computer	
			<b>4</b> I	89	Prose	
	r	Resident 3	<b>4</b> 7	100	Computer	
		·	37	79	Prose	
В.	Pros	e Format Fir	st			
	II	Staff	35	100	Prose	
			28	80	Computer	
	11	Resident 2	68	100	Prose	
			38	56	Computer	
	11	Resident 3	35	100	Prose	
		<b>5</b>	20	57	Computer	

required by the typist to transcribe these reports. Table II shows the typing time comparisons for the prose and computer formats. The computer dictating format reduced typing time by 25 to 33 per cent for the 3 radiologists.

Table III shows the great saving in time that can be achieved by use of clerical aid in displaying films for rapid reading on an automated viewing device. Repeat reading

Table II

COMPARISON OF TYPING TIME FOR PROSE

DS. COMPUTER FORMAT

(12 cases)

Radiologist	_	ime (per cent)	Format		
Staff	83	1∞	Prose		
	63	76	Computer		
Resident 2	90	100	Prose		
	. 60	67	Computer		
Resident 3	60	100	Prose		
	45	75	Computer		

Table III

EFFECT OF CLERICAL AID AND FILM

DISPLAY ON READING TIME

Case	Radiologist	T	ime	Clerical
Group	Kadiologist	(min.)	(per cent)	Aid
I	Staff	63	100	Without
		31	49	With
I	Resident 2	91	100	Without
		41	45	With

bias was not present, since the single reading sessions were separated by 8 months. Time saved by clerk aid and automated viewing was about 50 per cent for staff as well as resident radiologists.

### CONCLUSIONS

The use of computer style dictation format considerably reduced the radiologist's time for interpretation and reporting compared to the traditional prose style dictation system. Clerk assistance in preselecting films for display and use of automated viewing devices greatly decreased the time required for interpretation and reporting by the radiologist.

These findings indicate that the radiologist's time can be more efficiently utilized in a reporting system based on a clerk assisted computer format.

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### REFERENCE

 Report to the Surgeon General, U. S. Public Health Service: Protecting and Improving Health Through the Radiological Sciences. Prepared by the National Advisory Committee on Radiation, April, 1966.

### REPORT I

ROENTGENOGRAPHIC FINDINGS AND DIAGNOSIS PORTIONS OF TRADI-TIONAL PROSE FORMAT REPORT

### EXCRETORY UROGRAM

The renal transplant soft tissue density is present in the left iliac fossa and mea-

sures about 16.2 cm. in length. Previous roentgenograms since the recent transplantation are not available for comparison as to change in renal size. No opaque calculi are demonstrated. Bony structures again show the changes of diffuse generalized loss of bone density and changes of aseptic necrosis involving the femoral head bilaterally. Again previous roentgenograms are not available.

Following the injection of contrast material, there is slight delay in contrast excretion with subsequent delineation of the collecting system and proximal portion of the ureter by 15 minutes. The collecting system and ureter are slightly full. The distal ureter is not demonstrated. There is extravasation of contrast-laden urine laterally and inferiorly with impingement of the urine collection on the left lateral superior aspect of the bladder. Also contributing to the imprint is the inferior margin of the transplanted kidney. The bladder is only partially distended but is intrinsically grossly normal.

Impression. 1. Mild hydronephrosis and hydroureter with leak of urine presumably

from the ureter at the site of previous uretero-ureteral anastomosis.

### REPORT II

SAME CASE AS IN REPORT I WITH PERTINENT INFORMATION IN COMPUTER STYLE FORMAT

SIGNIFICANT ROENTGENOGRAPHIC FINDINGS

### Excretory Urogram

- 1. transplanted kidney, left iliac fossa; 16.2 cm. long
- 2. mild delay (10 min.) in contrast excretion
- 3. slight fullness of collecting system and ureter
- 4. extravasation of contrast-laden urine, presumed from mid-ureter at anastomosis
- 5. bilateral femoral head cortical fractures with compression

### Roentgenographic diagnosis

- I. mild hydronephrosis and hydroureter in renal transplant
- 2. ureteral anastomosis leak
- 3. bilateral femoral head aseptic necrosis



# TRANSLUMINAL EXTRACTION OF CATHETER AND GUIDE FRAGMENTS FROM THE HEART AND GREAT VESSELS; 29 COLLECTED CASES\*

By CHARLES T. DOTTER, M.D., JOSEF RÖSCH, M.D., and MARCIA K. BILBAO, M.D. PORTLAND, OREGON

THE initial report on flow-guided catheterization included a prediction that "careless or inadvertent motion could result in severance of the tubing and embolization, a complication which has not yet arisen, but will likely emerge as a specific hazard if the method receives widespread application." True. Based on collected case reports, 1.5.8-19.22.24.26-30.32-35 the lives of at least 100 patients have now been imperiled by broken-off bits of tubing or catheter guides\* lying within the lumen of the heart and great blood vessels.

The complication is serious; of 62 cases of catheter embolization collected by Bernhardt *et al.*, removal was not done in 28, and 17 of these died of related sepsis, perforation, thrombosis, arrhythmias or myocardial necrosis. Removal of the foreign body is effective; no death was reported in any of the 34 cases where it was done.

Although prompt removal of central catheter emboli is nearly always indicated, surgery should be considered only when safer and faster retrieval cannot be effected by transluminal catheterization. Clearly it often can, for it has already been done at least 29 times: in 19 reported cases, 8-11,15, 17-19,22,26-28,30,33,34 in 8 others about which we have learned, 12-14,24,29,32,35 and in 2 of our own patients.

### REPORT OF CASES

UOMS No. 432819 (Case 28 in Table 1). In a 21 year old female with septic abortion and suspected pulmonary embolization, a 3 inch length was inadvertently sheared off the tip of

a polyethylene CVP catheter. Roentgenograms made the following day faintly showed one end of the tubing lying in a right hepatic vein and the other against the medial wall of the right atrium above the tricuspid orifice (Fig. 1A). A 12 Fr thinwalled teflon catheter† was percutaneously passed via a femoral vein to the right atrium over a temporarily placed 8 Fr guide catheter. A doubled length of thin (4 Fr) teflon tubing was then passed through the 12 Fr catheter so as to create a closed loop in the right atrium (Fig. 1B). When the simple loop failed on 2 attempts to engage the fragment, several inches of the snare tubing were advanced so as to form a redundant, complex loop within the atrium (Fig. 1C). On the initial retraction of this loop, the target was snared and snubbed down against the end of the 12 Fr catheter so that, bent double, it could be slipped out of the patient in a matter of seconds (Fig. 1D).

UOMS No. 412263 (Case 29 in Table1). In a 63 year old female with suspected pericarditis, a leak developed close to the needle of a teflon polyethylene CVP tube placed via the right subclavian vein. The needle and adjacent damaged tube were cut off and a smaller catheter inserted through the remaining tube. Although the latter was taped to the skin, it nevertheless crept away silently during the night. Chest roentgenograms disclosed it lying wedged between the apex of the right ventricle and the lateral wall of the right atrium. As in the first of our 2 cases, a redundant loopsnare percutaneously inserted through the right femoral vein was used to remove the errant 8 cm. fragment. Initial failure to catch the end of the fragment wedged against the right atrial wall was overcome by temporarily replacing the loop with a tip-deflector guide,† which was used to shift the target into a more favorable position,

† Cook, Inc., P.O. Box 1272, Bloomington, Indiana 47401.

<sup>\*</sup> Broken catheter guidesprings were involved in only 6 of the 100 cases and have ceased to be a problem with the use of safety guides.<sup>6</sup>

<sup>\*</sup> From the Guttman Institute for Vascular Research through Radiology, University of Oregon Medical School, Portland, Oregon. Aided by USPHS Grants HE 03275, 01682 and 05828. With the technical support of Harold Kidd, Research Assistant.

Table I capansluminal retrievals of catheter debris from heart and great blood vessels as of July 4, 1970

Case No.	, Source and Reference	Age, Sex	Nature and Length of Foreign Body	Location of Foreign Body	Recovery Instrument	Recovery Route, Vein (Artery) Used
				,		
	7	JK 0	City Comment (Comment)	PA SVC	Bronchosconic forscns	Sanhenous cutdown
ч	I nomes of al."	40 IV	Guidespring traginent (9 cm.)	210 171	or the last of the	D franchist and antidomin
d	Lassers and Pickering <sup>15</sup>	43 M	Guidespring fragment (3 cm.)	Aorta at D II	Stone pasket-Loruna	n iemorai are cutdown
c.	Massumi and Ross <sup>17</sup>	¥ 8	Polyethylene CVP catheter, cut by needle (20 cm.)	RV-SVC	Loopsnare-homemade	K saphenous cutdown
7	Smyth et al.28	73 M	Polyethylene CVP catheter, fragment (23 cm.)	RA (coiled)	Bronchoscopic forceps	R ext. jugular cutdown
۲ ۷	Conradua	, t	Cardiac catheter (8 cm.)	. KA	Bronchoscopic forceps	R int. jugular cutdown
n V2	Hammermeister and Kennedyte	Z Q	Polyethylene CVP catheter, cut by needle	R SubclHep. V	Loopsnare-homemade	R brachial cutdown
1 (	Ramo et al #	1 % Y	Pacemaker catheter fragment	IVC	Loopsnare-homemade	R saphenous cutdown
~ oc	Henley and Ballardu	Z OS	Polvethylene CVP catheter, cut by needle	RV-SVC	Loopsnare-homemade	R int. jugular percutan.
	Falchuk et al.	W Q	Pacemaker catheter fragment (14 cm.)	IVC	Loopsnare-homemade	R femoral cutdown
Ņ	Miller of al.18	88 M	Polyethylene CVP cathleter, cut by needle (20 cm.)	RPA (coiled)	Loopsnare-Cook, Inc.	R brachial percutan.
: =	Miller of al. 18	7. F	Polyethylene CVP catheter, cut by needle (23 cm.)	LPA	Loopsnare Cook, Inc.	R subclavian percutan.
13	Shander	8.	PE tubing, (50 cm.)	RV-SVC	Stone basket-Dormia	R ext. jugular cutdown
	Shandern' Vonelts	6. Fr	Polvethylene CVP catheter, cut by needle (15 cm.)	RA, RV	Stone basket-Dormia	L arm cutdown
7 1	Edelstein	7 or	Polyethylene CVP catheter, cut by needle (20 cm.)	L SubclRA	Stone basket-Dormia	L basilic cutdown
ì	Soni et al. 30	14 M	PE IV catheter, cut by needle (20 cm.)	L SubclRV	Stone basket—Dormia	Arm v. cutdown
191	Rossins	72 M	Polyethylene CVP catheter, fragment	RA, RV (loop)	Hooksnare—homemade	R saphenous cutdown
17	Rossin	43 M	Polyethylene CVP catheter, fragment (40 cm.)	RA, RV, PA	Hooksnare homemade	R saphenous cutdown
· 81	Miller et al. 19	7 X	Polyethylene CVP catheter, cut by needle (13 cm.)	RA	Loopsnare—Cook, Inc.	R femoral percutan.
i oi	Tatsumi and Howland	4 mo. F	Holter valve, distal segment	RA	Loopsnare—Cook, Inc.	R int. jugular cutdown
8	Howland	W	Holter valve, distal segment	RA, RV	Loopsnare-Cook, Inc.	R int. jugular cutdown
17	Steiner and Kima	54 M	Polyethylene CVP catheter, cut by needle (42 cm.)	RV, R-LPA (coil)	Stone basket Mitchell	Arm v. cutdown
53	Ranniger	ì	Guidespring fragment	Desc. Thor. Aorta	Special catheter	Periph, art. cutdown
53	Kennedow	93 M	Polvethylene CVP catheter, cut by needle (15 cm.)	L SubcL-SVC	Loopsnare homemade	L arm v. cutdown
î	Humagel, Conradia	45 F	Cardiac catheter (8 cm.)	RA	Bronchoscopic forceps	R int. jugular cutdown
7 7	Hufnagel, Gomest	7. W	Polyethylene CVP catheter, cut by needle (14 cm.)	RA (coiled)	Bronchoscopic forceps	R int. jugular cutdown
96	Hufnagel, Conradia	36 F	Polvethylene CVP catheter, cut by needle (12 cm.)	RA	Bronchoscopic forceps	R int. jugular cutdown
27	Sonita	<b>W</b>	Polyethylene CVP catheter, fragment	RPA-LPA	Variflex catheter-Dormia	Arm v. cutdown
` 86 61	UOMS No. 432819	21 F	Polyethylene CVP catheter, cut by needle (8 cm.)	RA-Hep. V	Redundant loopsnare	R femoral percutan.
67	UOMS No. 412263	63 F	Polyethylene CVP catheter, cut by MD (12 cm.)	RA, RÝ	Redundant loopsnare	R femoral percutan.

RA-right atrium; RV-right ventricle; SVC-superior vena cava; IVC-inferior vena cava; PA-pulmonary artery; RPA-right pulmonary artery; LPA-left pulmonary artery.

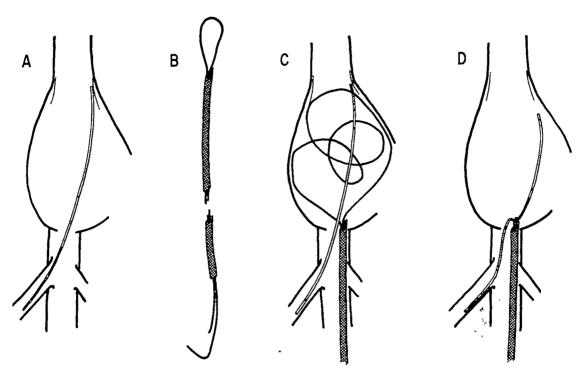


Fig. 1. Percutaneous transluminal retrieval of catheter embolus to right atrium, using redundant loopsnare. UOMS 432819, Case 28 in Table 1. (A) An 8 cm. fragment in right atrium and hepatic vein. (B) Homemade loopsnare catheter, long 4 Fr loop through 12 Fr outer sleeve; both radiopaque teflon. (C) One convolution of a redundant loop has caught the foreign body. (D) Fragment securely held and about to be removed via inferior vena cava and right femoral vein.

permitting its prompt capture by the reinserted redundant loop-snare. A gentle curve in the end of the 12 Fr outer sleeve would have made this extra step unnecessary.

### RECOVERY TECHNIQUES

The nonsurgical, transluminal retrieval of embolized catheter fragments and related intravascular foreign bodies is not only feasible, but is becoming commonplace. Including ours, 29 published or personally reported instances of nonoperative recoveries (Table 1) have added to our knowledge of how to do it—and more importantly—how to avoid the need for doing it. Several techniques have been used successfully; the most commonly employed instruments being loopsnares, grasping forcepts, and basket retrievers (Fig. 2, A-C).

Loopsnare catheters (Fig. 2A), varied in design but similar in function, have been responsible for 13 foreign body recoveries.

Portsmann's successful use of the loopsnare technique in 52 consecutive patients undergoing transluminal closure of patent ductus arteriosus 30,21 offers convincing confirmation of the value of the approach. Snare catheters are flexible, long-reaching, and suitable for percutaneous use. Not only is there a snare catheter based on a design by Curry<sup>8,4</sup> commercially available\* but such snares can easily be put together on an ad hoc basis, using materials ordinarily on hand wherever catheterization is done. Both design and manner of use can be tailored to the specific problem at hand. We believe that our use of a compound, convoluted loop within the right atrium facilitated catching the foreign body in both of our patients. Within limits, if one loop will do it, more loops will do it sooner; especially where poor visibility impedes

<sup>\*</sup> Cook, Inc., P.O. Box 1272, Bloomington, Indiana 47401.

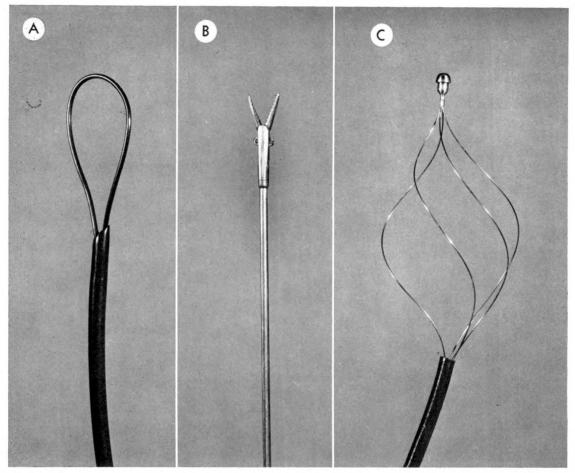


FIG. 2. Three retrieval devices used successfully in the cardiovascular system. (A) Homemade teflon adjustable loopsnare used in both our cases. Not shown but desirable—a gentle curve at the end of the outer catheter. (B) Bronchoscopic grasping forceps, of limited use, because of rigidity and short length. (C) A larger-than-urologic version of the basket stone catcher. With further modifications, this instrument will be used as an all-purpose transluminal extractor of particular value in catching nonopaque tubing and nontubular foreign bodies, and in the transjugular extraction of common duct stones.

precise three-dimensional control over the snaring maneuver. In place of a closed loop, Rossi<sup>26</sup> has reported 2 recoveries made with a flexible, preformed hook-ended snare. This approach, in addition to requiring cutdown, is presumably limited to the recovery of long segments of soft tubing, coiled or otherwise oriented at right angles to the axis of retrieval.

Bronchoscopic forceps (Fig. 2B) with alligator jaws were used in 6 recoveries. Rigidity and short reach limit the use of these instruments to certain applications; notably, the extraction of radiopaque objects from the right atrium via a surgically ex-

posed right jugular vein. Ranniger<sup>23</sup> has devised a flexible catheter which incorporates both a loopsnare and 3 grasping prongs; it has been used to recover a fragment of guide spring from the right ventricle.<sup>24</sup>

Ureteral stone baskets (Fig. 2C) have been successful in 7 recoveries. Soni et al.<sup>29,30</sup> have reported 2 recoveries using a Dormia ureteric stone basket.

The more complex retrieval in a 60 year old man involved the use of a controllable-tip catheter to withdraw the fragment of a polyethylene CVP catheter from the main pulmonary artery into the subclavian vein,

after the percutaneously inserted Dormia\* retriever had proved too short to reach the fragment at its original location (bridging the pulmonary artery, with its ends in the right and left main pulmonary arteries). A Variflex catheter with Pilotip guide and Muller Rotoflector† handle snared the fragment, which then became trapped as it was maneuvered into the subclavian vein. The Variflex catheter was withdrawn and replaced with the Dormia retriever for a successful extraction.

With the aid of William A. Cook, we have devised a similar instrument for use in the cardiovascular system, larger in expanded form and incorporating additional helicoid wires. It can be introduced percutaneously, using a thinwalled sheath, and should prove effective, particularly in fishing for non-radiopaque tubing and foreign bodies such as bullets.

Devices and tactics such as the foregoing can be used to remove objects from sites other than the vascular and urinary systems. Loopsnares have already been used to extract foreign bodies from the bronchial tree; <sup>19</sup> and via a burr hole, from the lateral ventricle. <sup>12</sup> We have used a specially designed side-operating snare to grasp and deliver from the jejunum an impacted fragment of Miller-Abbott tube<sup>2</sup> and are hopeful a catheter extraction technique can be successfully used for the nonsurgical transjugular removal of common duct stones.

### COMMENT

Every recovery implies a prior loss. To the best of our knowledge, all foreign bodies recovered from the vascular lumen by catheter were put there in the first place by physicians. Steiner et al., 31 Ross 25 and others have pointed out that embolization of plastic intravenous tubing is an avoidable complication of generally unrecognized magnitude. At least one variety of tubing (thin, radiopaque, polyethylene or teflon) is designed to be inserted through an ac-

\*Endoscopic Instrument Co., London, England. † U.S. Catheter and Instr. Corp., Box 787, Glens Falls, New York 12801. companying needle; the needle is then withdrawn from the vein and both it and the tubing are taped to the patient's skin. Despite clearly stated instructions and precautionary measures stressed by the manufacturer, the introducing needles have cut off and thereby launched fragments of tubing on hazardous voyages to the hearts of many patients. Shearing has often been caused by inadvertent motion of the sleeping patient. Better patient care is unquestionably facilitated by the literally millions of such units used with safety each year. On the other hand, while nothing designed to be put into patients will ever be foolproof, there are safety-designed alternatives which eliminate contact between needle and tubing.

### CONCLUSIONS

- I. Catheter emboli to the heart and great vessels can and should be promptly removed by the percutaneous transluminal route.
- 2. This has been done successfully at least 28 times by various means, the simplest of which is the loopsnare catheter.
- 3. In certain circumstances, the formation of a redundant, compound loop may be useful.
- 4. A specifically designed cardiovascular retrieval catheter based on the ureteral stone basket may prove to offer the best all-purpose approach to this increasingly important problem.
- 5. Safety-oriented, prepackaged intravenous intubation sets offer means for reducing the incidence of catheter embolization.

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### CATHETER RETRIEVAL OF FOREIGN BODY FROM THE GASTROINTESTINAL TRACT\*

### CASE REPORT AND DISCUSSION

By MARCIA K. BILBAO, WILLIAM W. KRIPPAEHNE and CHARLES T. DOTTER PORTLAND, OREGON

WHILE catheter retrieval of foreign bodies from the vascular system is becoming almost commonplace,<sup>1</sup> to our knowledge there have been no reports of similar retrievals from the gastrointestinal tract. We recently had occasion to apply the principles of vascular catheter retrieval to a retained intestinal tube and in the process encountered inherent differences in the mechanics of the situation and its management which seem worthy of reporting.

### REPORT OF A CASE

The patient, a 36 year old man, had undergone numerous operations for the relief of intestinal obstruction and lysis of adhesions due to childhood appendix and peritonitis. During the most recent of his operations, a long intestinal tube stent was placed by nasogastric route to the distal ileum. The first postoperative night the patient irrationally tried to pull out the tube; and failing this, chopped it off at his nose with a razor blade. What was left promptly recoiled downstream. Roentgenograms made during the ensuing 3 weeks showed the head of the tube fixed in the distal ileum and its cut tail just beyond the ligament of Treitz (Fig. 1, A and B). Although the patient was sent home from the hospital on a regular diet, the tube stubbornly stayed put. A barium study indicated that an ileal stricture was causing the hang-up (Fig. 1C). In view of an understandable surgical reluctance to enter again this adhesion-frozen abdomen, it was decided to try to remove the tube transluminally from above. To this end we modified a commercially available duodenal intubation set\* by attaching a loop snare to the tip of the guide and removing the metal tip from the catheter so as to leave it open-ended. This was passed without diffi-

\* Cook, Inc., P.O. Box 1272, Bloomington, Indiana 47401.

culty into the proximal jejunum, but repeated attempts to snare the tube failed. Although by overlapping the two (Fig. 2A), we could align the business end of our tube with the tail of the retained tubing, the two tubes moved apart each time we tried to approximate their ends (Fig. 2B). Based on the evident inherent mechanical situation, we then cut a slot in the side of the retrieval tube through which the snare loop, slightly bent for the purpose, could be pushed out (Fig. 3). With 10 inches of the two tubes overlapping (Fig. 2C), the snare was pushed out its window and over the tail of the target (Fig. 2D). With the patient's tube snugged tightly against ours, both were hauled up together—4 feet of ours and 10 feet of his.

### COMMENT

Failure of the initial end snare was due to the fact that the patient's tube took a configuration imparted by the small intestine in which it lay, while the recovery tube was under the influence of the stomach and duodenum. Only by overlapping the two tubes for some distance could they be brought into a stable approximation, thereby allowing the side loop to snare the target.

Other retrieval systems might also have been effective. It is possible that a modification of the basket ureteral stone catcher would work well in the redundant, floppy bowel. While long intestinal tubes uncommonly lead to gastrointestinal impasses, adhesion-frozen abdomens (making surgical exploration difficult) are not rare, nor are undesirable foreign bodies in the gastrointestinal tract. It seems reasonable to expect that many, if not all, bezoars could be broken up and removed via catheter; most solid objects small enough to be swal-

<sup>\*</sup> From the Departments of Diagnostic Radiology and Surgery, University of Oregon Medical School, Portland, Oregon. Aided by USPHS Grants GM 01682 and HE 03275. With the technical support of Martin and Norine Dietrich.

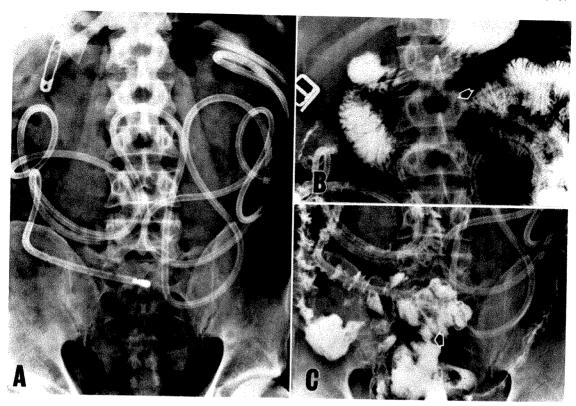
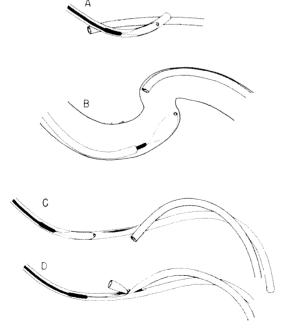


Fig. 1. (A) Barium study showing 10 feet of retained intestinal tubing. (B) The tail is near the ligament of Treitz (arrow). (C) The tip lies next to a structure in the distal ileum (arrow).



lowed could be retrieved promptly from the stomach, obviating the uncertainty, risk and delay often involved in relying upon an exit pathway most suitable for soft material. Convinced that foreign bodies other than in the gastrointestinal tract or vascular system can also be removed without surgical exposure if fluoroscopic visualization and suitable instruments are at hand, and spurred on by the success just reported, we recently undertook to extract a retained

Fig. 2. (A) End-exiting snare-guide and catheter lined up overlapping target. (B) Snare opposite target but now malaligned. (C) Side-exiting snare-guide and catheter lined up overlapping target. (D) Snare-guide has captured the target.

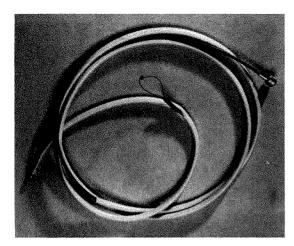


Fig. 3. Modified duodenal intubation set with side-exiting snare-guide.

subdiaphragmatic Penrose drain fragment. When attempts to retrieve it by catheter via a sinus tract failed, the patient was given a long forceps and allowed to take it out himself while watching the television monitor! Scheduled operation was avoided.

### SUMMARY

A 10 foot long retained intestinal tube fragment was removed by catheter from the jejunum using a duodenal intubation guide/catheter set modified by the addition of a side-exiting loop snare. Using modern fluoroscopy and appropriate catheter retrieval techniques, any foreign body small enough to swallow but unsuitable or unsafe for normal passage can probably be easily removed through the lumen of the upper gastrointestinal tract.

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## ROENTGENOLOGIC ASPECTS OF CARDIAC TRANSPLANTATION\*

### POSTOPERATIVE PULMONARY INFECTIONS

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THE importance of infectious complications in the immunosuppressed host following renal transplantation has previously been emphasized. 10,11,17 Preliminary data attest to a comparable frequency of infectious complications following cardiac transplantation. 6,9 The purpose of this report is to describe our experience at Stanford University Medical Center with pulmonary infections in 10 of 18 patients undergoing cardiac transplantation. Particular attention is given to the roentgenologic aspects of these infections with emphasis on the value of frequent roentgenologic study in postoperative management.

### MATERIAL AND METHOD

Eighteen patients, 15 males and 3 females, underwent cardiac transplantation. The ages ranged from 33 to 64, with an average of 50 years. Five patients had idiopathic cardiomyopathy and the remainder end-stage ischemic heart disease. Pulmonary hypertensionwas present preoperatively in 11 of 12 patients undergoing cardiac catheterization, with an average calculated pulmonary vascular resistance of 5.8 resistance units. Preoperative pulmonary function studies were abnormal in 6 of 7 patients studied.

The operative methods have been previously described.<sup>21</sup> In all cases a median sternotomy incision was employed. Ventilatory assistance was afforded postoperatively to all patients for periods up to 24 hours. Tracheostomy was performed in only the first 2 patients.

All patients received as basic immuno-

suppression therapy azathioprine and prednisone or methylprednisolone. Antilymphocyte globulin was used for varying periods postoperatively in all but the first 2 patients. Details of maintenance immunosuppressive therapy and treatment for rejection are described elsewhere.<sup>20</sup>

Sputum, urine, and stool cultures for bacteria and fungi were obtained preoperatively in all patients. Sputum cultures were obtained 3 times weekly for the first postoperative month and then less frequently. Transtracheal aspirates for smears and cultures were obtained promptly in all patients at times of suspected pulmonary infection. Prophylactic antibiotics, consisting of penicillin, methacillin, and streptomycin or cephalothin, were begun at the time of surgery and continued for only the first 2 to 3 postoperative days. These were continued for I week in I patient in whom coagulase-positive staphylococci were isolated preoperatively from the sputum (Case 18).

Reverse isolation with hospital personnel wearing caps, masks, shoe covers, and sterile gloves and gowns was employed for up to 2 weeks postoperatively. After this period masks and hand washing only were utilized for the remainder of the hospitalization. When patients were able to have studies in the X-Ray Department, no special precautions were taken other than a mask worn by the patient. Daily postoperative chest roentgenograms were obtained until patients were ambulatory and, thereafter, at least twice weekly until the time of discharge. Serial tomography was

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performed on several patients with pulmonary lesions. Five percutaneous needle aspiration lung biopsies under fluoroscopic control were performed in 3 patients (Cases 4, 13, and 17) for diagnosis of pulmonary lesions.<sup>5,19</sup>

The pre- and postoperative chest roentgenograms were correlated with the clinical course and laboratory information regarding infectious complications. Specific roentgenologic characteristics of the various infections were noted.

### RESULTS

Ten of the 18 patients undergoing car-

diac transplantation developed pulmonary infections, for a total of 15 separate infectious episodes. The clinical data concerning these patients are summarized in Table I. From these 10 patients a total of 25 organisms were isolated from the tracheal aspirates or lung biopsy specimens during clinical evaluation or were observed at autopsy. Bacteria were the most common infecting agents and accounted for 14 infections, of which 9 were gram negative, 3 gram positive, and 2 mixed anaerobic. The only fungus encountered, Aspergillus, caused 5 infections. Cytomegalic virus was observed 3 times, Pneumocystis twice, and

TABLE I
PULMONARY INFECTIONS IN CARDIAC TRANSPLANT PATIENTS

Case No.*	Age and Sex	Organism(s)	Postoperative Day	Diagnostic Technique	Outcome‡
1	54M	Klebsiella Aspergillus	8	Tracheal Aspirate Autopsy	Terminal (15 days postoperative)
2	40M	I O	***************************************		Expired (3 days postoperative: pulmonary hypertension)
3	<sub>4</sub> 2M	Pneumocystis C.M.V.† Klebsiella	42	Tracheal Aspirate Autopsy Autopsy	Terminal (46 days postoperative)
4	51M	Bacteroides (probable)	5.5	Needle Biopsy	Cured and alive (16 mo. postoperative)
5	54F		3.3		Expired (31 mo. postoperative: hepaticoma)
6	54F	E. coli Bacteroides Aspergillus Pneumocystis Toxoplasma C.M.V.†	63	Tracheal Aspirate Autopsy Autopsy Autopsy Autopsy Autopsy Autopsy	Terminal (65 days postoperative)
7	54M	Mixed anaerobic bacteria	36	Tracheal Aspirate	Cured
,	21	Klebsiella	73	Tracheal Aspirate	Cured and alive (14 mo. postoperative)
8	56M	and the same of th	T O		Expired (22 days postoperative: cerebra vascular accident)
9	$_{49}M$	Klebsiella	27	Tracheal Aspirate	Cured
		Staphylococcus coagulase+	52	Tracheal Aspirate	Cured
		Staphylococcus coagulase+	99	Tracheal Aspirate	Cured but expired (91 mo. postoperative rejection)
10	43M	Mixed anaerobic bacteria	62	Tracheal Aspirate	Cured and alive (10 mo. postoperative)
11	56M		-	•	Expired (10 days postoperative: rejection
12	42M		*****	*******	Expired (39 days postoperative: rejection
13	58M	Proteus morganii	51	Tracheal Aspirate	Cured
		Aspergillus	84	Needle Biopsy	Under treatment (9 mo. postoperative see text)
14	34M	Automore	and the same of th	et-max.	Alive (7 mo. postoperative)
15	51M	and the same of th		*****	Expired (4½ mo. postoperative: rejection)
16	54M		Washing.	and the same of th	Expired (10 hr. postoperative: pulmonar; hypertension)
17	44F	Aspergillus	42	Needle Biopsy	Under treatment (3½ mo. postoperative)
18	64M	Staphylococcus coagulase+	31	Tracheal Aspirate	Cured
		Aspergillus Klebsiella	43	Tracheal Aspirate Autopsy	Terminal (2 mo. postoperative)
		C.M.V.†		Autopsy	

<sup>\*</sup> Case numbers refer to number held in current Stanford cardiac transplant series.

<sup>†</sup> C.M.V. = Cytomegalic Inclusion Virus.

<sup>&</sup>quot;Terminal" indicates death due to infection. "Expired" indicates death due to other causes, as noted.

Toxoplasma once. In 4 patients pulmonary infection was due to multiple organisms (Cases 1, 3, 6, and 18) and in these cases identification was made at autopsy.

As of this writing 6 of the 18 patients undergoing transplantation are alive. Of these, 5 were treated successfully for one or more episodes of pulmonary infection or are presently undergoing treatment. Five of 12 expired patients had pulmonary infections and, in 4 of these 5 patients, the infection was considered to have directly contributed to death (Cases 1, 3, 6, and 18).

With the exception of I patient (Case I), all episodes of infection occurred at least 4 weeks postoperatively. Nine of the 13 patients who survived for longer than I month had at least I pulmonary infection.

Organisms were recovered from all 5 aspiration biopsies done on 3 patients. In Cases 13 and 17 the aspirated material grew Aspergillus, although simultaneous sputum and tracheal aspirate cultures were negative. In these 2 patients repeat aspiration biopsies were performed at the time of insertion of a small catheter for treatment of the pulmonary cavities. Aspirated material from the third patient (Case 4) revealed small gram negative rods which did not grow in culture.

### ROENTGENOGRAPHIC FINDINGS

Roentgenologic manifestations of pulmonary infection were present in 14 of the 15 infectious episodes. In 12 of these there was roentgenographically demonstrable pulmonary disease corresponding to the clinical findings. In 2 cases of pulmonary aspergillosis the roentgenographic findings were present prior to clinical evidence of infection (Cases 13 and 17). In one case Staphylococcus aureus was isolated from a tracheal aspirate at a time of clinical illness without roentgenographic abnormality (Case 18).

Bacterial infections manifested primarily as large segmental infiltrates or consolidations. Cavitation was noted in 2 of these cases, both due to anaerobic organisms (Cases 4 and 7; Fig. 1). The third patient with an anaerobic infection (Case 10; Fig.

2) initially demonstrated a nonspecific upper lobe nodular density which subsequently cavitated. Associated pleural disease was seen only once in a patient with a loculated empyema (Case 4). Diffuse bilateral infiltrates were present in 3 instances (Cases 1, 3, and 6; Fig. 3 and 4) and were seen shortly before death. In each of these cases multiple organisms were recovered at autopsy, although only 1 organism was recovered pre mortem by tracheal aspiration.

All 3 instances of isolated Aspergillus infection diagnosed ante mortem showed cavitation on chest roentgenograms. In 2 patients (Cases 17 and 18) bilateral discrete nodular densities rapidly appeared with cavitation occurring in most of the nodules within a week. The third patient (Case 13; Fig. 5, A-D) demonstrated cavitation in a right upper lobe nodule and in an adjacent infiltrate.

Hilar and/or mediastinal lymphadenopathy was not roentgenologically identified in any patient.

### DISCUSSION

"Opportunistic" infections have increased in importance and frequency.<sup>1,2,8,12</sup> These infections are caused by many types of primary pathogenic as well as saprophytic organisms showing enhanced virulence due to alteration in the host's capacity to resist infection. Numerous disease states and conditions predispose.15 The high incidence of pulmonary infections in our cardiac transplant recipients presumably relates primarily to immunosuppressive therapy. The mechanisms involved in the diminution of the host's resistance to infection include both altered reticuloendothelial function and humoral antibody response.18,14,22 It appears unlikely that altered pulmonary status alone accounts for the increased susceptibility to infection since a comparable incidence is not noted in patients undergoing nontransplant cardiac surgery. However, the combined effects of preoperatively abnormal pulmonary function, pulmonary hypertension, thoracotomy, and prolonged postoperative me-



Fig. 1. Case 7. Posteroanterior upright chest roentgenogram (41 days postoperative). Large cavitating infiltrate in the left upper lobe. Mixed anaerobic bacteria were isolated from the trachea. The infiltrate completely resolved with therapy.

chanical ventilation cannot be excluded as contributing significantly to the pathogenesis of postoperative pulmonary infections.

Renal transplant recipients constitute a comparable group of patients treated by similar immunosuppressive regimens. Active pulmonary infections were noted at autopsy in 33 of 39 patients with renal homografts. Numerous causative organ-

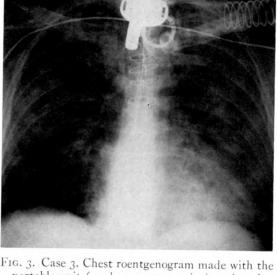


Fig. 3. Case 3. Chest roentgenogram made with the portable unit (44 days postoperative), 2 days before death, demonstrating bilateral diffuse infiltrates. *Pneumocystis* was isolated ante mortem. *Klebsiella* and *Cytomegalic inclusion virus* were observed at autopsy.

isms were present including gram negative rods, Candida, Aspergillus, Nocardia, Pneumocystis carinii, and Cytomegalic virus. In more recent reports, fungal infections were



Fig. 2. Case 10. Posteroanterior upright chest roentgenogram (64 days postoperative). Relatively well-defined left upper lobe nodular density and ill-defined right apical infiltrate. Mixed anaerobic bacteria were isolated by tracheal aspiration. As the infiltrates resolved with therapy, the left upper lobe density underwent cavitation.

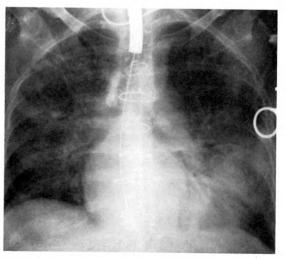


Fig. 4. Case 6. Roentgenogram made with the portable unit (65 days postoperative), shortly before death. Bilateral patchy infiltrates and a large area of consolidation at the left base. Pneumocystis, Aspergillus, Toxoplasma, Cytomegalic inclusion virus, and Bacteroides were found at autopsy. E. coli had been cultured from a tracheal aspirate 2 days before this roentgenogram.

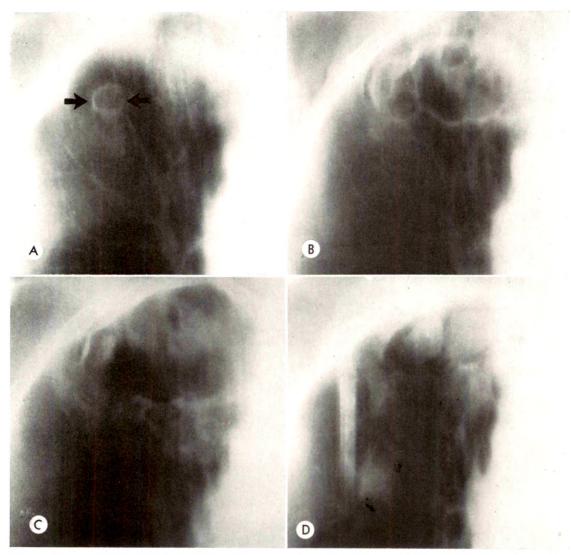


Fig. 5. Case 13. Serial tomograms of the right upper lobe. (A) At 78 days. A 1×1.5 cm. thin-walled cavity (arrows) is associated with a large adjacent apical infiltrate. Aspergillus was recovered by percutaneous needle aspiration of the cavity. (B) At 107 days. The cavity now measured 5×8 cm. and involved the entire apex, despite 3 weeks of systemic amphotericin B administration. (C) At 134 days. Continued increase in size of the cavity with extension inferiorly. Following this roentgenogram, a treatment catheter was inserted (see text). (D) At 226 days. Marked decrease in size of cavity (3×5 cm.) after 3 months of intracavitary therapy with amphotericin B and sodium iodide. Two mycetomas ("fungus balls") are present. A new nodular infiltrate is noted at the inferior aspect of vertical artifact (due to blurred needle hub).

seen in approximately half of the autopsied patients<sup>17</sup> and pulmonary infections by multiple organisms were often present.

A clinical syndrome of unknown etiology, "transplant lung," has been described in renal transplant recipients. Roentgenograms demonstrate perihilar and lower zone infiltrates which do not resolve with anti-

biotic therapy but usually respond to increased dosages of corticosteroids. We have not observed this entity in the cardiac transplant recipients.

Goodman *et al.*,<sup>7</sup> correlated roentgenograms with pathologic data at autopsy in 45 renal transplant recipients. When only single organisms were present, local alveo-

lar consolidation indicated bacterial disease; cavities correlated best with fungal disease. Our experience has been similar, although cavitation occurred in 3 patients with anaerobic bacterial pneumonias. While the roentgenographic appearance may often suggest an etiology, there is no roentgenologic specificity. Definitive diagnosis can only be obtained by identification of the infecting organisms.

All infectious episodes (with the exception of Case 1) occurred at least 4 weeks post transplantation. After 1 month, any roentgenologic pulmonary abnormality, other than vascular congestion, was associated with pulmonary infection. A high index of suspicion of even minor abnormalities should be maintained, as strikingly rapid progression of disease was characteristic of virtually all these infections.

Prompt diagnosis and initiation of specific therapy are critical in the effective treatment of infections in the immunosuppressed host. Sputum cultures are often inadequate, particularly when normally saprophytic organisms and multiple pathogenic agents are present.3,17 In our patients tracheal aspiration was initially employed to establish a diagnosis. When these cultures were negative, percutaneous aspiration biopsy under fluoroscopic guidance was productive as a source of both cytologic and culture material. The technique has been demonstrated previously to have excellent diagnostic accuracy. The small percentage of serious complications<sup>5,19</sup> is a readily acceptable alternative to open lung biopsy.

Another application of the percutaneous aspiration technique<sup>4</sup> involves the direct instillation of appropriate drugs into a fungal cavity in an effort to locally eradicate infection without producing systemic toxicity. In 1 patient (Case 13; Fig. 5, A-D) following aspiration of material for culture, a small polyethylene catheter was passed through the needle into the cavity and sutured to the skin. Irrigation of the cavity with amphotericin B and sodium iodide 3 times weekly has been performed

for the past 4 1/2 months. The cavitated area has decreased to approximately one-third of its previous size without signs of systemic drug toxicity. In a second patient (Case 17) local treatment of a 3×2 cm. cavity was discontinued after 3 days because of technical problems.

### SUMMARY

Pulmonary infections occurred in 10 of 18 patients undergoing cardiac transplantation at the Stanford Medical Center and contributed to the death of 4 patients. A variety of organisms have been responsible including both aerobic and anaerobic bacteria, fungi, protozoa, and viruses.

Although the roentgenographic findings were nonspecific, bacterial pneumonias were generally associated with local infiltrates or consolidations, while cavities were present in all instances of isolated aspergillosis. The value of frequent roentgenograms is emphasized since, after the first postoperative month, all pulmonary abnormalities other than vascular congestion were caused by infection.

The value of needle aspiration lung biopsies for establishing a diagnosis is emphasized. Application of this technique for direct intracavitary antifungal therapy has been apparently successful in 1 patient to date.

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### LIPIODOL ACCUMULATIONS SIMULATING LUNG METASTASES AS COMPLICATION AFTER LYMPHOGRAPHY\*

By Dr. T. DE ROO ALKMAAR, THE NETHERLANDS

ALTHOUGH in lymphographic examination the oily contrast medium flows via the thoracic duct into the venous blood stream, it can lead to the development of multiple small pulmonary emboli which on chest roentgenograms are visible as small spots.

This occurrence does not give rise to clinical symptoms and the miliary shadows on the chest roentgenogram disappear within a few days. Serious symptoms of oil emboli are rare. It is true that pulmonary capillaries may get obstructed, but this obstruction is of a temporary nature and thus the supply and breaking down of the oil can remain in balance.

Usually a chest roentgenogram is made immediately after lymphography, not so much to demonstrate eventual miliary shadows of the lung, but to complete the examination, for it is important to establish that after the examination the patient is returned to the clinician for further treatment without complications. It is logical, of course, that a chest roentgenogram made immediately before the lymphographic examination should be available for comparison. One may be in for an unpleasant surprise if the chest roentgenogram made previous to lymphography is missing for some reason or other. Following are 2 cases in point.

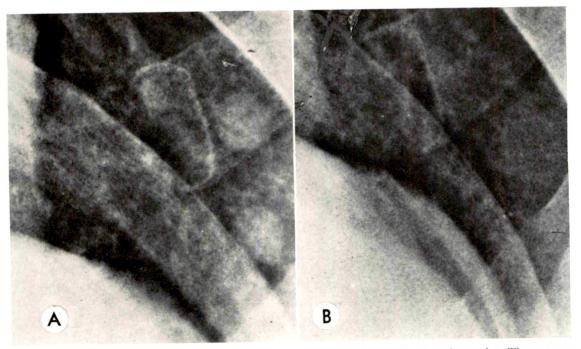


Fig. 1. (A and B) Lipiodol accumulations simulating lung metastases after lymphography. There are 2 sharply defined round dense configurations in the lower left lung field (A). The supposed pulmonary metastases have disappeared in a few weeks (B).

<sup>\*</sup> From the Department of Radiology, Central Hospital, Alkmaar, The Netherlands.

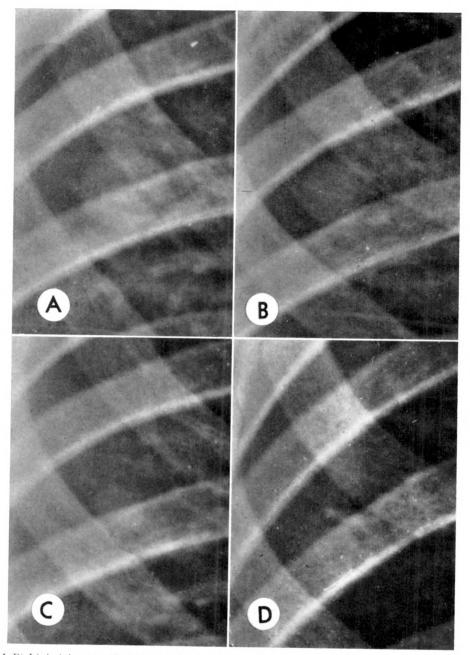


Fig. 2. (A-D) Lipiodol accumulations simulating lung metastases after lymphography. One sharply defined round density is noted in the right upper lung field (A). On follow-up, the density became smaller after 2 days (B) and 3 days (C), respectively, and finally disappeared in 4 days (D).

### REPORT OF CASES

Case I. A left orchiectomy was performed on a 51 year old patient for a tumor of the testis consisting of a teratoma and embryonic carcinoma. Immediately after operation a lymphography was performed to either demonstrate or

exclude metastases. On the lymphogram left paralumbar metastases were seen in the lymph nodes. On the chest roentgenogram made after the lymphographic examination, no miliary shadows, but sharply defined round dense configurations with a diameter of 1 to  $1\frac{1}{2}$  cm. were

visible in the upper right and lower left (Fig. 1A) lung field. The roentgenologic diagnosis was pulmonary metastases, and it was decided not to operate upon this patient. On the chest roentgenogram made some weeks later the supposed pulmonary metastases had disappeared (Fig. 1B). The round densities in the lung resembling metastases must have been caused by an accumulation of lipiodol, which is very rare. In this context, it should be recorded that the total amount of contrast medium used, namely 16 ml. (8 ml. per extremity), and the speed of injection of 1 ml. per 10 minutes were normal. A lymphaticovenous anastomosis through which an abnormal amount of contrast oil could have flowed directly to the lung, could not be demonstrated. If a chest roentgenogram had been taken immediately before the lymphographic examination, this diagnostic error could not have been made, for, of course, eventual metastases would have been visible on both chest roentgenograms.

That this peculiar type of accumulation of lipiodol in the lung was not an isolated manifestation is indicated by the following case.

Case II. A lymphography was performed on a I4 year old girl suffering from a kidney tumor. No metastases could be demonstrated in the lymphatic system. In this case, too, the chest roentgenogram showed sharply defined round densities with a diameter of  $\frac{1}{2}$  to 2 cm. in the upper right (Fig. 2A), and middle left lung fields.

However, pulmonary metastases could be ruled out at once, because a chest roentgenogram made immediately before the examination did not reveal any abnormality of the lungs. On follow-up the peculiar accumulations of lipiodol became gradually smaller after 2 days (Fig. 2B) and 3 days (Fig. 2C), respectively, and finally disappeared altogether in 4 days (Fig. 2D).

### CONCLUSIONS AND SUMMARY

A rare complication after lymphographic examination is the appearance of accumulations of lipiodol in the lung simulating metastases.

These rather large sharply defined round densities in the lung were observed twice in over 1,000 patients examined by lymphography.

Although this is a very small percentage, it implies that it is not sufficient to have only a chest roentgenogram after lymphography; there should always be available a roentgenogram of the chest made immediately before the examination for comparison.

Erroneous roentgenologic diagnosis of lung metastases might lead to incorrect treatment of the patient.

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### ROENTGEN FEATURES OF GIANT CELL CARCINOMA OF THE LUNG\*

By ARCOT GAJARAJ, M.D., T. H. JOHNSON, Jr., M.D., and JOHN H. FEIST, M.D. PITTSBURGH, PENNSYLVANIA

GIANT cell carcinoma of the lung was accepted as a distinct histopathologic entity, since its first description by Nash and Stout<sup>12</sup> in 1958.

Twelve cases were studied in retrospect and the radiologic findings were correlated with the autopsy findings. The available clinical autopsy and radiologic data of other reported cases in the literature were also reviewed. We have attempted to assess distinguishing roentgen criteria for the diagnosis of giant cell carcinoma of the lung.

The characteristic histopathologic ap-

pearance is a rapidly growing, anaplastic and pleomorphic lesion with bizarre multinucleated giant cells. The incidence is in a younger age group, with a propensity for metastasis and a fulminating course. While the clinical and pathologic features have been reviewed extensively in the literature, there has been no report of the radiologic manifestations.

### CLINICAL OBSERVATIONS

In the 12 cases studied there were 11 males and 1 female (Table 1). The ages varied from 45 to 76 years, with the maxi-

TABLE I SUMMARY OF FINDINGS

Case No.	I	2	3	4	5	6	7	8	9	10	11	12	Total 12 Cases
Clinical Data													***************************************
Age	50	45	60	76	64	50	61	51	64	60	51	49	56.8*
Sex	M	M	M	M	$\mathbf{M}$	F	M	M	M	M	M	Mı	1 M; 1 F
History of smoking	+	+	+	+		+	+	_	+	+	+	+	10
Occupation	Ex	Ex	Ċ	Ċ	Ex	Ex	Ex	S	$\mathbf{E}\mathbf{x}$	Ex	Ex	Ċ	
Clinical presentation													
Respiratory			+	+	_	+	+	_	+	+	+	_	7
Metastatic	+	+		<u>.</u>	+			+	<u>.</u>		<u>.</u>	+	Ś
Total duration of illness	·	•			•			•				•	,
in months	4	12.3	6.5	1.6	3.75	10	5	3	8	2.5	5.8	2.5	5·4*
Roentgen Features													
Size in cm.	1/2	10	10	3	3.5	10+	4	6	10+	4	4	4	5·75 <b>*</b>
Lung involved	Ŕ	R	L	Ř	R	R	Ŕ	Ĺ	L	Ŕ	Ŕ	Ĺ	8 R; 4 L
Location													,
Periphery	_	_	+	+	+	+		-	_	+	+	+	7
Hilar	+	_			<u> </u>			+	+		<u>.</u>	_	3
Indeterminate	_	+	*****	-	_		+	_	<u>.</u>			_	2
Cavitation	_		+	+	+		÷	_		+	-	+	6
Pleural involvement	_	+	+	+	÷	+	+	+		÷	+	+	10
Chest wall involvement	_	<u>.</u>	÷	÷	_	_	_	_		+	_	_	3
Hilar lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	12
Mediastinal lymph nodes	<u>.</u>	÷		+	+	÷	+	+	+	+	+	<u> </u>	10
Distant metastasis	+	÷		÷	÷	÷	-	÷	÷	÷	+	÷	IO

Ex=Executive. C=Coal miner. S=Steel worker. R=Right lung. L=Left lung. +=Positive. -= Negative.

<sup>\*</sup> Represents average figures and the rest indicates number of cases.

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mum incidence between 45 to 60 years, and an average of 56.8 years. A history of smoking cigarettes for a duration of 15 to 35 years was available in 9 cases, and 1 patient was a pipe smoker. Three were coal miners, 1 a steel worker and the other patients were executives.

In 5 patients the presenting symptoms were neurologic, due to intracranial metastasis. The primary lung lesion was detected in these cases on routine chest roentgenograms. Among the 7 cases with pulmonary symptoms 6 had a history of cough (1 dry, 1 productive, 3 associated with hemoptysis, and 3 with chest pain). Two patients had dyspnea and wheezing.

The evolution of the disease process from the date of first consultation to death of the patient was very rapid despite treatment (Fig. 5, A and B). The duration of illness varied from 2 weeks to 3 months at the time of first detection. The survival after diagnosis ranged from 10 days to 3 months in 9 cases and in the other 3, it was 4, 6 and 8 months, respectively. The total duration of illness varied from 1.6 to 12 months and was within 5 months in 7 cases. The average clinical course was 5.4 months.

# ROENTGEN FEATURES

All lesions were rounded or lobulated opacities varying in size from  $\frac{1}{2}$  cm. to as much as 10 cm. in over-all diameter (Fig. 1–5). Two of them presented as dense patches of consolidation with superadded infection. For purposes of statistics they were taken roughly as 10 cm. in diameter. In 7 cases the tumor was located in the peripheral lung field, 3 were of the hilar type and in 2 it was difficult to evaluate the exact site of origin since the lesions were extensive involving both the hilus and periphery.

Cavitation could be detected in 6 cases (Fig. 1; 3; and 5, A and B). Pleural involvement and progressive effusion was present in 10 cases (Fig. 2, A and B; and 4). In 3 of these, invasion of the chest wall was observed (Fig. 1). In 1 case there was a spontaneous pneumothorax (Fig. 4).

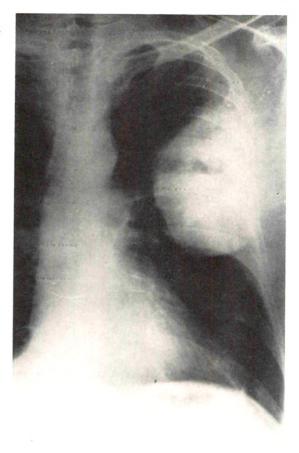


Fig. 1. Case 3. Massive peripheral opacity in the left lung, showing cavitation, fluid level and chest wall involvement.

Hilar lymph node enlargement was observed in all cases without exception. The mediastinum was enlarged in 10 cases. Distant metastasis was present in 10 cases at the time of medical attention. In 5 of these, the presenting symptoms were due to metastasis to the brain. In 3 of the latter, angiographic and/or pneumoencephalographic evidence of intracranial space-occupying lesion was present.

# REVIEW OF LITERATURE

Nash and Stout<sup>12</sup> are credited with the identification of giant cell carcinoma of the lung as a distinct histopathologic entity. The clinical and pathologic data of the cases reported were analyzed and compared (Tables II and III). This study represented

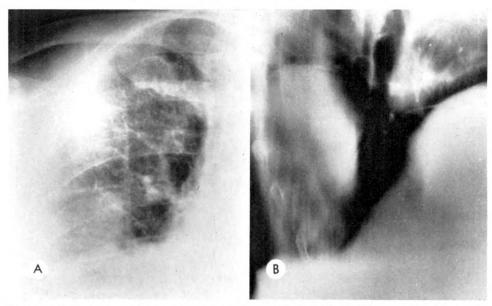


Fig. 2. Case 4. (A) Posteroanterior roentgenogram. (B) Right lateral laminagram. Massive opacity in the periphery of the posterior basal segment of the right lower lobe with pleural involvement.

a review of 63 cases including our 12 cases. The average age was 55.2 years. The sex incidence in 46 cases was 39 males and 7 females. History of smoking was documented in 48 cases. The mode of clinical presentation as seen in 46 cases was pulmonary in 33 and due to metastasis in 9. Cough was a prominent symptom in 25 cases, while in 20 cases chest pain was predominant; 15 cases presented with both. Eleven had hemoptysis: in 9 cases dyspnea was present. The clinical course from detection to death in 59 cases averaged 5.6 months.

From the description of the macroscopic appearances of the autopsy specimens, it was observed that the average size of tumor varied from 4.1 cm. in diameter to more than 10 cm. The majority of the lesions were massive and measured more than 5 cm. Among 45 cases, where the location of the tumor was known, 32 were in the peripheral lung field, whereas only 9 were of the hilar type. In 4 the exact location could not be assessed. Although the upper lobes were affected in a good number of cases, the superior sulcus was not involved in any case. The presence of cavitation was observed in 27 cases. Pleural involve-

ment with effusion was observed in 34 cases. In 34 cases the hilar lymph nodes were involved, and in 32 mediastinal involvement was present. Distant metastasis was observed in 55 cases. Of these, in 9 cases the presenting symptom was due to metastasis.

# DISCUSSION AND DIFFERENTIAL DIAGNOSIS

The place of radiology in the diagnosis of carcinoma of the lung has been well illustrated by Rigler, 14 in 1955. It has also been documented that certain cell types have specific roentgen findings. 8 The significance of cell types to clinical course and prognosis has been discussed. 5,10

Giant cell carcinoma of the lung forms a distinct histopathologic group. It comprised 3.4 per cent of all primary carcinomas of the lung in the series of Hellstrom and Fisher.<sup>4</sup> It was observed from our study that it has certain distinguishing roentgen features. The tumor was common in males (85 per cent) and in smokers (76.2 per cent). It was peripherally located in most cases. Cavitation was a significant sequel. Pleural involvement with pleural effusion was a prominent feature. The hilar

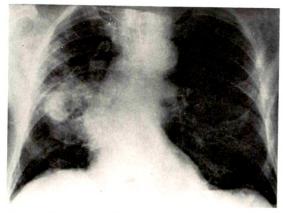


Fig. 3. Case 7. Peripheral lesion with cavitation of the mid zone of the right lung. Hilar and mediastinal lymph node involvement is indicated by the pressure effect on right main bronchus with decreased volume of the right hemithorax.

lymph nodes were invariably involved and mediastinal spread was frequent. Distant metastasis was very common. Rigler, <sup>15</sup> has drawn attention to the long symptomless period that may occur in peripheral carcinomas of the lung. The lesion was nevertheless progressive from the date of diagnosis with a fulminating clinical course. The average duration of life was 5.6 months after detection.

Thus, it is observed that giant cell carcinoma of the lung has a few characteristic roentgen features. The peripheral location

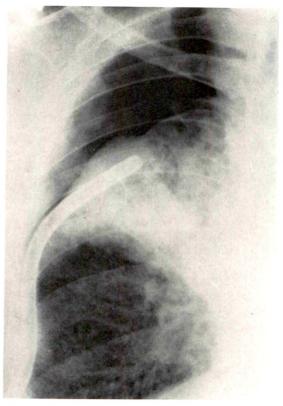


Fig. 4. Case 11. Peripheral lesion of the right lung extending into and involving both the hilus and pleura with spontaneous pneumothorax.

of the tumor, early hematogeneous metastasis, and a comparatively rapid growth, resemble adenocarcinoma. But the male pre-

TABLE II
CLINICAL FINDINGS

Name of Authors	Year	No. of Cases	Age* (yr.)	Sex		History	Clinical Presentation			Average Duration
							Respi-	Meta-	Asymp-	of Illness
				M	F	Smoking	ratory	static	tomatic	(mo.)
Nash and Stout <sup>12</sup>	1958	5	5 I	4	I	3	3	_	2	4 for 4 cases
Hellstrom and Fisher <sup>4</sup>	1963	17	52.I			16	_		_	4.6 for 15 cases
Oberman and Danilovic <sup>13</sup>	1964	I	78	I	_	_	I			2.7 for I case
Flanagan and Roeckel <sup>1</sup>	1964	4	54.3	4	_	.3	3	I		3.81 for 4 cases
Metropol et al.9	1965	2	60.5		2	_	2	_		6 for 2 cases
Friedberg <sup>2</sup>	1965	2	64.5	I	I	I	2			3.6 for 2 cases
Kovalik and Callaghan <sup>6</sup>	1965	I	52	I		I	I			_
Guillan and Zelman <sup>3</sup>	1966	12	58	I 2	_	I I	ΙI	I		6.4 for 12 cases
Munetomo <sup>11</sup>	1966	I	33	I			I			10 for 1 case
Lerner <sup>7</sup>	1967	6	55.3	4	2	3	2	2	2	9.1 for 6 cases
Gajaraj <i>et al</i> .	1969	12	56.8	ΙI	I	IO	7	5	_	5.4 for 12 cases
Average or Total Number of Cases		63	55.2 for 63 cases	39	7	48	33	9	4	5.6 for 59 cases

<sup>\*</sup> Represents average figures and the rest indicates number of cases.

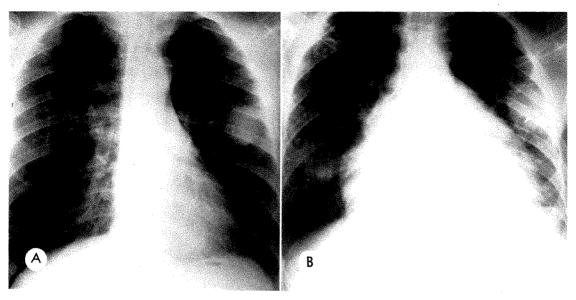


Fig. 5. Case 12. (A) Initial roentgenogram. (B) Roentgenogram 1 month later. Rapid progression of an umbilicated peripheral nodular lung lesion with cavitation, pericardial and phrenic nerve involvement. The left dome of the diaphragm is raised with occlusion of the left costophrenic angle.

ponderance, relationship to smoking and to differentiate.

Although extensive involvement of the the frequency of pleural involvement help hilar and mediastinal lymph nodes may simulate the appearances of a primary

TABLE III AUTOPSY ROENTGEN FEATURES

Name of Authors	Year	Lung Involved		Size of	Location of Tumor				Lymph Nodes		Pleural	Distant
		R	L	Tumer* (cm.)	Periph- ery	Hili	Indeter- minate	Cavita- tion	Hili	Medias- tinum	Involve- ment	
Nash and Stout <sup>12</sup>	1958	3	2	7.5 for 5 cases	3	ı		4	4	**************************************	4	5
Hellstrom and Fisher <sup>4</sup>	1963	6	11	5.35 for 17 cases								15
Oberman and Danilovic <sup>13</sup>	1964		I	8 for 1	1	*****	-Parameter	I	1		1	ī
Flanagan and Roeckeli	1964	3	1	4. I for 4 cases	1	3		2	4	4	4	4
Metropol et al.9	1965	I	1		2		111100		2		2	
Friedberg <sup>2</sup>	1965	2		10 for 2	¥.	1			I	2		2
Kovalik and Callaghan®	1965	i		10 for 1	I	******					I	
Guillan and Zelman³	1966			7.8 for	9	1	2	12	9	Э	9	12
Munetomoli	1966	I		10 for 1	1			1		I	I	1
Lerner <sup>7</sup>	1967	4	2		6			ī	I	2	2	5
Gajaraj et al.	1969	8	4	5.75 for 12 cases	7	3	2	б	12	10	10	10
Average or Total Number of Cases		29	22	6.46 for 55 cases	32	9	4	27	34	32	34	55

<sup>\*</sup> Represents average figures and the rest indicates number of cases.

anaplastic growth of a major bronchus, these are rarely peripheral in location, and necrosis and cavitation are not usual.

The epidermoid carcinoma is not necessarily confined to the major bronchi and may present as peripheral or subpleural masses. It may resemble giant cell carcinoma by tendency for cavitation, and the prevalence in males and smokers. It is, however, confined to the lung parenchyma and the regional lymph nodes for a considerable time. Hematogeneous metastasis is late. The age incidence is in a later decade, 60 years. The prognosis is more favorable.

Alveolar cell carcinomas are also peripherally situated. They occur as discrete nodular masses or as pneumonia-like forms. They differ from giant cell carcinomas by the rarity of pleural involvement and their slow growth rate.

The adenomas (cylindromas and carcinoids) are relatively benign and extend over decades. Curability with surgery is high.

Lymphosarcoma of the lung is a rare lesion. It is usually massive involving a lobe or entire lung. Pleural involvement is not a prominent feature.

Fibrosarcoma is again a rare tumor of the lung producing massive lesions. There is no hilar or mediastinal lymph node involvement.

The mesotheliomas are mediastinal or peripheral lesions affecting the pleura. Calcification occurs frequently. Post-thoracentesis roentgenograms may reveal the pleural growth.

# SUMMARY

Twelve cases of giant cell carcinoma of the lung were studied in retrospect. The roentgen features were correlated with the clinical and autopsy findings.

The clinical, autopsy and available radiologic data of 51 other cases reported in the literature were also analyzed and studied to assess the size, location, and the local or distant spread.

It is concluded that giant cell carcinoma of the lung has a few specific roentgen features which may be helpful to differentiate this lesion from other pulmonary neoplasms.

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# THE FISSURE SIGN: ITS MULTIPLE CAUSES

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THE perfusion lung scan measures re-THE periusion rung seem gional pulmonary arterial blood flow by the particle distribution method. 21,24,25 Normally with intravenous injection of radioactively labeled macroaggregates in a supine patient, the distribution of radionuclide throughout the lung fields will be uniform. This uniformity of radiopharmaceutical distribution is manifest by a homogeneous pattern of radioactivity over each lung. Abnormal perfusion patterns characteristic of various diseases have been described. One strikingly abnormal pattern is a linear band of decreased or absent radioactivity which occupies the position and has the configuration of the interlobar fissure.14 Originally described in association with multiple small pulmonary emboli, this finding has been termed the "fissure sign." This perfusion pattern is not specific for pulmonary microemboli, but may result from other pulmonary diseases. We have collected from 4 institutions examples of the "fissure sign" and will discuss our experience with the multiple causes of this pattern.

# PLEURAL FLUID AND PLEURAL THICKENING

The most common clinical setting for the "fissure sign" in a general patient population is in association with pleural fluid. This pattern will be especially frequent if the pulmonary perfusion images are obtained in the supine position. In the upright position, pleural fluid does not pass far distal in the interlobar fissure by capil-

lary action unless a large amount of subpulmonic fluid is present. With a large subpulmonic effusion, the pleural fluid extends laterally and passes up into the interlobar fissure.4 This ascent of interlobar pleural fluid must involve most of the length of the interlobar fissure because the corresponding band of decreased radioactivity on the lateral perfusion image extends from the diaphragm to the dorsal surface of the lung. The presence of significant pleural fluid may be detected on the lung scan by lack of angularity of the peripheral area of radioactivity (Fig. 1, A-C). This corresponds to "blunting" of the costophrenic angle on the chest roentgenogram. Fluid may also be suspected from the lung scan by homogeneous changes in perfusion due to position changes for the various views.3 If images are obtained with patients supine, the mediastinum will appear widened on the posterior view. This is probably a result of fluid dissecting into this area due to the patient's position. Analysis of patients with pleural fluid on chest roentgenograms revealed that approximately 70 per cent will have a "fissure sign" on lung scans.

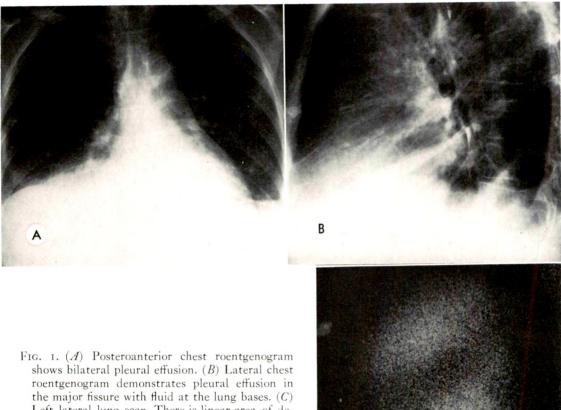
It has been commonly observed that pleural effusions occur with pulmonary embolism. The presence of the "fissure sign" with an obvious pleural effusion, therefore, does not lower the probability of the diagnosis of pulmonary emboli. 10 Pleural effusion and the "fissure sign" may be seen in association with congestive heart failure and pulmonary edema (Fig. 2, A and B). In this instance, the pulmonary perfusion scan

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Left lateral lung scan. There is linear area of decreased radioactivity corresponding to the left interlobar fissure with diminished radioactivity at the lung base posteriorly.

may show a distribution of radionuclide which is nonhomogeneous but without perfusion defects that correspond to the anatomic segments of the lung.6 With pulmonary venous hypertension associated with pleural effusion, the "fissure sign" may be seen concomitantly with increased radioactivity in the upper compared to the lower lobes.6 This reversal of pulmonary artery perfusion pattern is a manifestation of physiologic changes that occur in pulmonary venous hypertension.

The chest roentgenogram is essential in detecting thickened pleura as a cause of the

"fissure sign." Supine and decubitus roentgenograms in these patients fail to demonstrate changes in the widened pleural markings with change in position. This increase in width of the interlobar pleura is too generalized to represent fluid loculation. Therefore, we have interpreted these roentgenograms as "pleural thickening." There may or may not be associated slight blunting of the costophrenic angles. The chest roentgenogram obtained concomitantly with the lung scan must reveal a prominent major fissure on the same side as the "fissure sign."

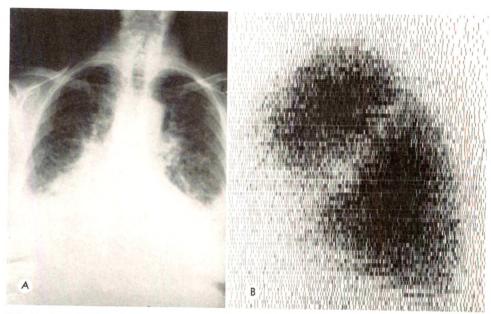


Fig. 2. (A) Posteroanterior chest roentgenogram shows pulmonary edema with bilateral pleural effusions. (B) Left lateral lung scan reveals linear area of diminished radioactivity corresponding to the interlobar fissure.

# CHRONIC LUNG DISEASE

Patients with a history of chronic productive cough, abnormal lung function studies (such as forced expiratory volume in one second—FEV1) and chest roentgenographic findings of chronic lung disease will occasionally have a "fissure sign" on perfusion lung scans. There is often no roentgenographic evidence of pleural thickening and no pleural effusion is seen. The associated pattern of pulmonary perfusion will often show a nonsegmental, nonhomogeneous radionuclide distribution. The nonsegmental areas of hypoperfusion are more distinct than those seen in congestive heart failure and pulmonary edema, but not so distinct as the segmental perfusion defects seen with pulmonary macroemboli. The perfusion abnormalities often are symmetric if one lung image is compared to the other. We have encountered patients with chronic lung disease who have minimal nonhomogeneity of radionuclide distribution but a rather prominent "fissure sign." The following patient is an example:

S. R., a 59 year old male, worked in a coal washing plant for 24 years and smoked 20

cigarettes a day for 25 years. He was admitted to the West Virginia University Hospital for evaluation of severe dyspnea on exertion and a productive cough.

Pulmonary function studies were characteristic of severe obstructive airway disease: total lung capacity 156 per cent and forced expiratory volume in 1 second 53 per cent of predicted normal. His residual volume occupied 62 per cent of his total lung capacity with an elevated airway resistance (twice normal). Arterial blood gases showed moderate hypoxemia at rest. Clinically the patient was unable to tolerate minimal exercise.

The posteroanterior chest roentgenogram showed minimal increased lucency of the lung fields, flattened diaphragms, and no evidence of pleural fluid (Fig. 3A). The pulmonary perfusion scans employing a rectilinear scanner, showed decreased activity in a configuration and location corresponding to the major fissure (Fig. 3, B-D).

Another chronic disease of the lung in which the "fissure sign" is seen on perfusion lung scans is in children with cystic fibrosis (Fig. 4, A-C). In 35 patients with proven cystic fibrosis seen at Children's Memorial Hospital, lung perfusion scintigrams revealed a definite "fissure sign" in

20 (Fig. 5, A and B). In this population, 5 additional lung perfusion scintigrams had linear zones of decreased radioactivity which suggested the "fissure sign."

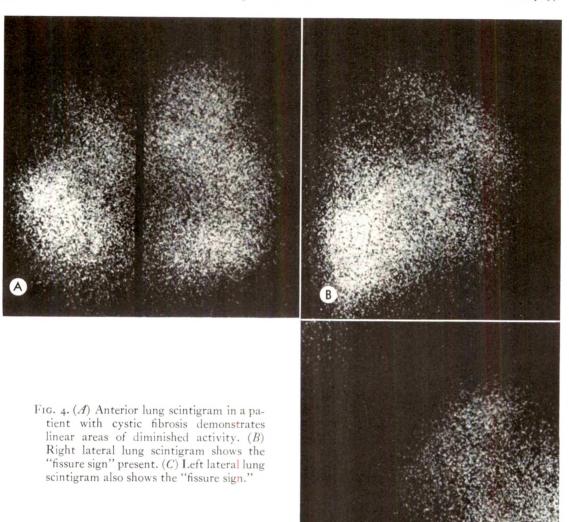
In all other forms of chronic lung disease the incidence of this scintigraphic finding is much lower in our experience, approximately 5 to 8 per cent. We have encountered examples of patients with the "fissure sign" that have been seen sporadically in rare causes of chronic lung disease, such as sickle cell anemia and collagen vascular diseases, but only mention these as unusual causes.

# PULMONARY MICROEMBOLI

Patients sometimes present with strong clinical evidence of pulmonary emboli,



Fig. 3. (A) Posteroanterior chest roentgenogram shows flattened diaphragm with minimal hyperlucency of lung fields. (B) Anterior lung scan demonstrates linear areas of decreased activity in position and configuration of the major fissure (arrows). (C) Right lateral lung scan shows the "fissure sign" (arrow) on the right. (D) Left lateral lung scan shows the "fissure sign" (arrow) on the left.



normal concurrent chest roentgenograms (including lateral decubitus roentgenograms), and no segmental perfusion defects but a "fissure sign" on the lung scintigram (Fig. 6, A–C). A few of these patients have come to autopsy shortly after perfusion lung scintigraphy<sup>8</sup> and were found to have multiple small pulmonary emboli.<sup>7,14,16,22,23</sup> Occasionally the "fissure sign" is seen on the lung scintigram associated with segmental perfusion defects in patients with normal chest roentgenograms.<sup>17</sup> In the right lateral scintigram both the major and minor fissures are sometimes seen in pa-

tients without roentgenographic evidence of pleural effusion, pleural thickening, or clinical evidence of chronic lung disease.<sup>10</sup> Three population groups in which multiple small pulmonary emboli appear to be more common are patients with macroemboli,<sup>11</sup> postoperative patients following cardiovascular surgery,<sup>2,26,27</sup> and patients with a history of recurrent episodes of shortness of breath. These latter patients often have such vague symptomatology that their disease is inappropriately labeled as "asthma" or "viral illness."<sup>19</sup>

The above descriptions of the "fissure

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# PROPER INTERPRETATION OF PULMONARY ROENTGEN CHANGES IN SYSTEMIC LUPUS ERYTHEMATOSUS

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MANY of the roentgen abnormalities in patients with collagen diseases have been thoroughly and carefully documented. However, the proper evaluation of pulmonary disease in systemic lupus erythematosus (SLE) still presents a formidable challenge. Previous radiologic studies have resulted in a variance of opinion regarding the true character of these lung changes.

In 1955 Gould and Daves<sup>6</sup> described focal patches of infiltration and linear plaques, generally in the lower lobes, in 50 per cent of their lupus patients. They felt that these abnormalities were caused directly by the underlying disease process. Nice and his colleagues<sup>10</sup> in 1959 found "interstitial pneumonitis" on chest films of 46 per cent of their patients. Alarcón-Segovia and Alarcón¹ have described both micronodular and infiltrative forms of "lupus pneumonitis," each occurring in 15 per cent of their cases.

The microscopic changes in the lungs of autopsied lupus patients have been discussed by Baggenstoss,<sup>2</sup> Harvey et al.,<sup>7</sup> and Huang et al.<sup>8</sup> These changes include a peculiar basophilic mucinous edema of the alveolar walls, hyaline membranes, focal necrosis, arteritis, hemorrhage and interstitial pneumonia. It is not entirely clear which of these processes were clinically significant and specific for SLE and which were terminal changes caused by infection, infarction, atelectasis, congestive heart failure, oxygen toxicity or any combination thereof.

The common feature of these studies is their implication that lupus patients frequently develop a specific or primary type of lung disease. Accordingly, the term "lupus pneumonitis" has come to be rather indiscriminately applied to all pulmonary complications of SLE.

A distinctly different opinion was expressed by Dubois and Tuffanelli<sup>5</sup> in their large clinical series in 1964. Only 0.9 per cent of their patients were felt to have lupus pneumonitis. They characterized this entity as infiltration in the lungs caused by vasculitis and persisting for weeks or months. Corticosteroids were the only helpful therapeutic agent. Thirty-one per cent of their cases developed bacterial pneumonias. Sullivan and Miller<sup>12</sup> also felt that recurrent pneumonias are a secondary complication of SLE, rather than a primary manifestation of the disease process.

In view of these discrepancies, a study was made of 111 SLE patients seen at the New York Hospital—Cornell Medical Center between 1965 and early 1970. Their chest roentgenograms and case histories were carefully analyzed. An attempt was made not only to catalogue the various types of roentgen changes, but also to determine their exact cause wherever possible.

# ROENTGEN FINDINGS

The most common abnormalities in this series were due to pleural disease. Of those with intrinsic lung parenchymal disease, most were due to secondary complications such as patchy atelectasis, superimposed infection or uremic pulmonary edema. Primary lupus pneumonitis occurred only very rarely. These various changes are discussed below.

# I. PLEURAL DISEASE

One of the most common manifestations of SLE is inflammation of the serous cavi-

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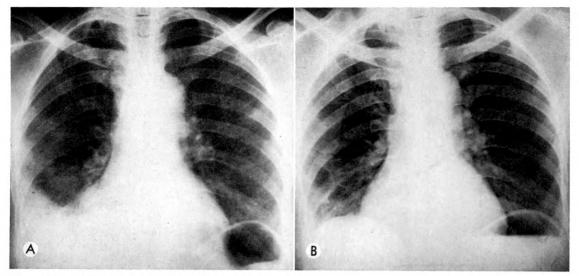


Fig. 1. Lupus pleuritis in a 51 year old female.

(A) Right pleural effusion, pain and fever were present at the time of admission. Twelve days of antibiotic therapy failed to produce improvement. (B) Seven days after discontinuing antibiotics and starting high dose prednisone therapy, the right pleural changes have almost completely resolved. The patient's temperature returned to normal almost immediately upon commencement of steroids.

ties of the thorax, primarily the pleura, but also the pericardium. Roughly one-third to one-half of all lupus patients develop pleuritis sometime during the course of their disease. 5.7 The presenting clinical symptoms are pleuritic pain and inability to breathe deeply. Chest roentgenograms typically show diaphragmatic elevation, a small pleural effusion and streaky lung parenchymal consolidation at the corresponding base. Occasionally the pleuritic pain occurs without effusion. Rapid clinical and roentgenographic improvement follows institution of high dose corticosteroid therapy.

It should also be remembered that pleural effusion can develop in patients who have lupus nephrosis. These individuals have no specific pleural inflammation but they do sometimes have large pleural effusions as part of the generalized anasarca which is characteristic of nephrotic syndrome.

These two types of effusions can generally be differentiated merely by the fact that lupus pleuritis is accompanied by pain and splinting, whereas the serous effusions of nephrosis are painless.

In our series of III patients, 33 developed pleural effusion during the course of their

disease and 5 more had clear symptoms of pleurisy without observable fluid accumulation. Figure 1, A and B is an example of lupus pleuritis in a woman with no renal disease. She improved rapidly with high dose steroid therapy. Figure 2 is a roent-genogram of another young woman with severe uremia and nephrosis due to SLE. Her pleural effusion, the largest in this series, was presumably nephrotic in origin since she had generalized anasarca but no pleuritic pain. Steroids were not helpful at

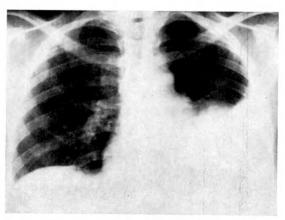


Fig. 2. Large painless left pleural effusion in an 18 year old female with severe lupus nephrosis.

this stage, although she did improve considerably on a vigorous diuretic regimen including ethacrynic acid and intravenous albumin.

# II. PATCHY ATELECTASIS

As indicated above, patients with lupus pleuritis generally exhibit diaphragmatic elevation, a small pleural effusion and streaky lung parenchymal consolidation at the corresponding base. Some authors have considered these basilar infiltrates to represent lupus pneumonitis, a proposition which is without any real justification. Since the patients usually have prolonged pleuritic pain, splinting and impaired ability to cough, a much more logical explanation is that the infiltrates actually represent patchy atelectasis. A familiar analogous situation occurs in the postoperative patient who develops basilar atelectasis after abdominal surgery because of pain and involuntary restriction of diaphragmatic excursions.

It was not possible to statistically quantitate the occurrence of basilar atelectasis since this area of the lung was frequently

found to be obscured by overlying pleural fluid. There is no doubt, however, that it does develop in a moderate number of individuals with active lupus pleuritis. Except for I patient with right lower lobe bacterial pneumonia, all cases of localized basilar infiltration were accompanied by pleural disease.

Figures 3, A and B, and 4, A-C are examples of patients having basilar atelectasis associated with lupus pleuritis. Both responded well to steroids with clearing of the infiltrates once normal breathing was restored.

Streaky basilar consolidation in SLE patients should thus be considered patchy atelectasis whenever there is clinical and roentgenographic evidence of concurrent pleuritis. Only if the chest roentgenogram shows a good deep inspiration and absence of pleural disease should another explanation be invoked.

# III. SUPERIMPOSED INFECTION

Superimposed pulmonary infection occurs frequently in SLE patients as a result

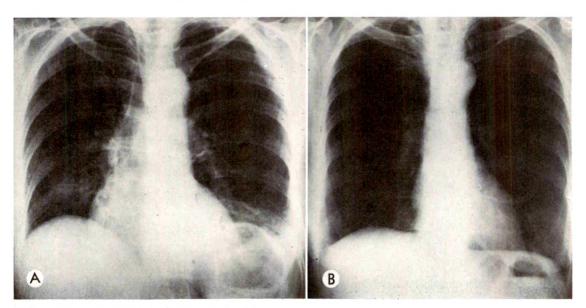
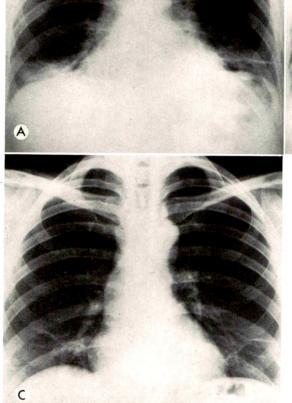


Fig. 3. A 61 year old female with lupus pleuritis.

(A) The streaky infiltration at the left base was felt to be due to patchy atelectasis since it was associated with pleuritic pain, effusion, poor cough mechanism and diaphragmatic elevation. (B) Two weeks after institution of steroid therapy the patchy atelectasis and pleural effusion have disappeared. Note more satisfactory inspiratory excursion of the diaphragm.



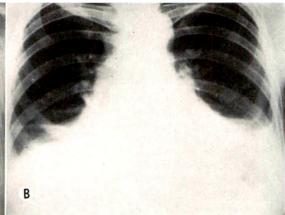


Fig. 4. A 34 year old female with bilateral lupus pleuritis.

(A) Admission roentgenogram showed streaky infiltration in both lower lobes. The patient could not breathe deeply due to severe pleuritic pain and these infiltrates were felt to represent patchy atelectasis. (B) Two days later pleural effusions have appeared bilaterally. (C) Four days after starting steroids there has been complete resolution of the pleural effusions. The parenchymal densities have resolved, except for a few small areas of residual platelike atelectasis.

of the basic alteration of the normal immune mechanism and the prolonged administration of corticosteroids. Sixteen New York Hospital patients developed this complication in the relatively early stages of their disease while still generally healthy. This does not include a number of others who acquired bronchopneumonia in the terminal stage. Eight of the 16 had bacterial pneumonias, 4 had tuberculosis and 4 had fungus infections. Figures 5, and 6, A and B are examples of the latter.

# IV. UREMIC PULMONARY EDEMA

Uremic pulmonary edema occurred in 4 patients in this series. This diagnosis is easily established by the combination of blood urea nitrogen elevation, clinical symptoms and characteristic roentgenologic

findings. The latter consist of vascular and interstitial congestion with fluffy alveolar infiltrates which are most pronounced in the perihilar areas and lower lobes. Pleural effusion and cardiac enlargement may or may not be present. Figure 7 illustrates this condition. Less frequently (1 patient in our series) congestive heart failure develops as a result of lupus myocardopathy.

# V. LUPUS PNEUMONITIS

After excluding patients having basilar atelectasis, superimposed pulmonary infection or uremic pulmonary edema (all considered to be secondary changes) it became readily apparent that primary, specific lupus pneumonitis is remarkably rare. Only 3 of 111 patients in this study appeared to be so afflicted. Because of its

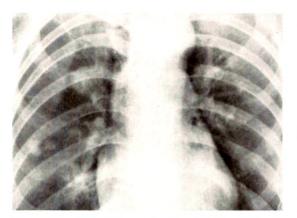
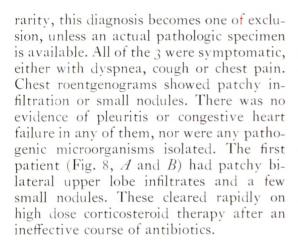


Fig. 5. Monilial abscesses in the right lung of a 27 year old female with systemic lupus erythematosus.



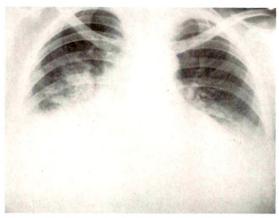


Fig. 7. Uremic pulmonary edema in a 17 year old female with advanced lupus nephritis and hypertension.

The second patient (Fig. 9, A-D) had 2 separate episodes, one manifested by bilateral interstitial infiltration and the other by unilateral miliary nodules. Rapid spontaneous clearing occurred in both instances.

The third patient (Fig. 10, A and B) died after developing extensive bilateral alveolar and interstitial infiltration which failed to respond either to antibiotics or steroids. Autopsy revealed severe disseminated pulmonary vasculitis with interstitial and alveolar hemorrhages and inflammatory exudates.

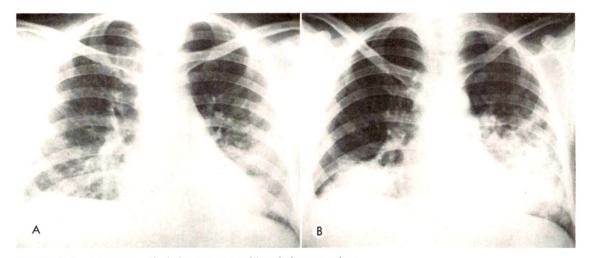


Fig. 6. Pulmonary nocardiosis in a 22 year old male lupus patient.

(A) Initial roentgenogram shows bilateral infiltrates. (B) Sixteen days later, progression and coalescence are noted. The patient expired shortly thereafter.

field, but the physical examination was otherwise unremarkable.

The hematocrit was 30 per cent, and the white blood cell count was 8,000 cells per mm.³, with a normal differential count. Numerous sputum and stool cultures were normal, and complement fixation and hemagglutination studies for *E. histolytica* were negative. Liver function studies were all within normal limits. The chest roentgenogram revealed the presence of a right basilar infiltrate without effusion (Fig. 6).

During the course of hospitalization, the liver increased in size and exhibited tenderness to palpation. Because of this finding the diagnosis of amebiasis was entertained, and the subsequent Au<sup>198</sup> liver scan demonstrated the presence of a filling defect within the right lobe of the liver adjacent to the right diaphragm (Fig. 7). The patient was treated with emetine and chloroquin, and within a 2 day period marked symptomatic improvement was apparent. The patient continued to improve, and was discharged from the hospital 2 months following admission, with no apparent sequelae.

Case v. This 34 year old Caucasian male was admitted to the hospital with a 4 day history of right pleuritic chest pain, fever, and vague right upper quadrant abdominal discomfort. He further admitted to cough productive of a clear mucoid sputum. The patient denied previous diarrhea or other gastrointestinal symptoms.

The initial hematocrit was 40 per cent, and the white blood cell count was 13,200 cells per mm.<sup>3</sup>, with a slight shift to the left. Sputum and

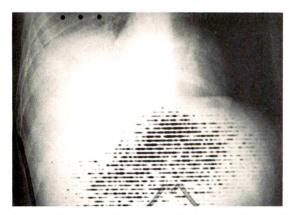


Fig. 5. Case III. Composite of the superimposed Au<sup>198</sup> liver scan and supine chest roentgenogram reveals the large filling defect within the right lobe of the liver, as well as the right basilar infiltrate with effusion.

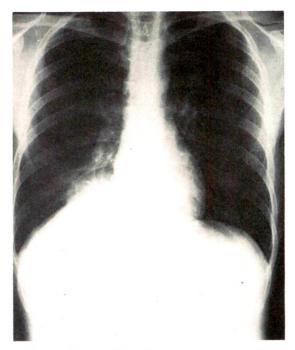


Fig. 6. Case iv. Frontal roentgenogram reveals right basilar infiltrate.

stool cultures were negative for parasites. The initial chest roentgenogram revealed slight elevation of the right diaphragm, as well as a poorly defined right lower lobe infiltrate without effusion. The initial complement fixation test for antibodies against *E. histolytica* was negative. However, a repeat study performed 8 days after admission was positive, with a titer of 1:1,024.

The patient was admitted to the hospital

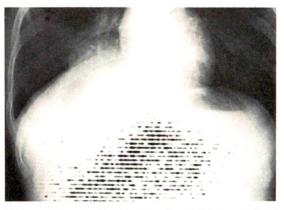


Fig. 7. Case IV. Composite of superimposed Au<sup>198</sup> lung scan and frontal chest roentgenogram demonstrates the presence of a large filling defect within the right lobe of the liver.

with symptoms consistent with a primary pulmonary process, and treatment was initiated with broad spectrum antibiotics. However, the finding of an elevated right diaphragm and right basilar infiltrate on chest roentgenogram, as well as the clinically evident hepatic tenderness suggested the possibility of amebiasis. This diagnosis was substantiated by serial serologic study, and definitive therapy with emetine and chloroquin was instituted. The patient was transferred to another hospital after 3 weeks for further study and convalescent care.

# DISCUSSION

Amebiasis is world-wide in distribution, and Bockus<sup>1</sup> notes an incidence of 8.1 per cent within the United States. The disease is produced by the tissue-destroying protozoan, Entamoeba histolytica, which has 5 stages in its life cycle: trophozoite, precyst, cyst, metacyst, and metacystic trophozoite. Only ingestion of the viable cyst will produce disease, as the trophozoite is readily destroyed by hydrochloric acid and peptic digestion within the stomach. The cysts of E. histolytica may remain viable in water for periods up to 30 days, but are killed by drying and temperatures over 50°C. Infection is due to ingestion of the viable cysts in contaminated food or drink.

During passage through the small intestine, the cyst evolves into the trophozoite phase. Within the cecum and ascending colon, the invasive trophozoites produce lytic digestion of the mucosa and submucosa, but the muscularis mucosae forms a relative barrier to their progression within the tissues. The lateral submucosal extension of colonies results in the characteristic flask-shaped ulcers within the colon. The cecum and right colon are most susceptible to involvement by the protozoan, while the rectum and sigmoid are second in incidence of involvement. Some colonies of E. histolytica may successfully penetrate the muscular layer of bowel wall, and produce lytic digestion of the walls of tributaries of the mesenteric veins. This provides the eventual pathway of metastasis to the liver and lungs, via the portal vein and inferior vena cava. Within the liver, the trophozoites

gain access to the portal sinusoids and produce amebic hepatitis and/or amebic liver abscess. Pleuropulmonary extension occurs in approximately 20 per cent of patients with amebic liver abscess.¹ Within the thorax, the involvement may be in the form of pulmonary consolidation, lung abscess, broncho-hepatic fistula, serous pleural effusion, empyema, or purulent pericarditis.8 Although the finding of trophozoites within the sputum or pleural fluid is diagnostic, in most cases it is not possible to recover the organism.8 The thoracic extension of the disease may be produced by any one of a number of theoretic mechanisms:8

- 1. Direct rupture of an amebic hepatic abscess through the diaphragm
- 2. Lymphatic spread through the diaphragm from an amebic hepatic abscess or hepatitis
- 3. Embolic spread of colonies of *E. histolytica* to the lungs from an amebic hepatic abscess, or directly from the colon to the lungs by hematogeneous dissemination via the inferior and middle hemorrhoidal veins, superior mesenteric vein, and inferior vena cava
- 4. Inhalation of dust containing cysts of *E. histolytica*. This mechanism is of questionable clinical significance.

A rare complication is invasion of the pericardium, with the production of amebic pericarditis. This dramatic manifestation of the disease occurs in less than 3 per cent of patients with amebic hepatic abscess.<sup>2</sup>

The clinical findings of amebiasis are variable. Patients with the intestinal form of the disease may present with acute amebic dysentery, which is characterized by chills, fever, malaise, abdominal cramps, and bloody diarrhea. Patients with chronic intestinal amebiasis may have intermittent periods of diarrhea, and some chronic cyst passers may be entirely asymptomatic. Pleuropulmonary extension of the disease may produce fever, chills, pleuritic chest pain, hemoptysis, expectoration, and the physical signs of pulmonary consolidation

or pleural effusion. A characteristic chocolate-colored or "anchovy-paste" expectoration will occur if there is extensive tissue necrosis, erosion into a bronchus, or the formation of a broncho-hepatic fistula.6-8 An important physical finding is the presence of tender hepatomegaly or deep palpation tenderness within the right upper quadrant of the abdomen. Pande and Srivastava<sup>8</sup> noted that the finding of an enlarged tender liver was eventually present in 95 per cent of their 22 patients with pleuropulmonary amebiasis. Patients with pericardial extension of the disease exhibit a variable clinical picture, and purulent pericarditis with acute tamponade may occur.<sup>2,6</sup> When pulmonary consolidation occurs, it is nearly always within the right lower lobe. Left basilar consolidation is usually secondary to either pericardial disease or extension from an abscess within the left lobe of the liver.6

Leukocytosis with a shift to the left is a fairly constant finding in patients with pleuropulmonary disease, and a mild eosinophilia may be present in up to 25 per cent of cases.8 It is especially noteworthy that Entamoeba histolytica is difficult to recover from samples of stool, pleural fluid, and sputum in patients with pleuropulmonary amebiasis. 5,6,8 Serologic tests have been developed to detect antibodies against E. histolytica, and are extremely helpful when positive. However, at the present time the complement fixation and serum hemagglutination tests are not entirely dependable, and the lack of demonstration of antibodies against the organism does not entirely exclude the diagnosis.<sup>1,3</sup>

The roentgenographic features of pleuropulmonary amebiasis are not specific for the disease. However, the combination of certain roentgenographic features with a suggestive history may allow the radiologist to venture the correct diagnosis. The spectrum of roentgen findings includes:<sup>4</sup> elevation of the right diaphragm; pleural effusion; lower lobe consolidation; and lung abscess. Elevation of the right diaphragm reflects the presence of an underlying hepatic abscess, although a secondary mechanism may be atelectasis and decreased volume of the right lower lobe. The right diaphragm is typically involved, due to the preponderance of amebic abscesses within the right lobe of the liver. 6,8 The transdiaphragmatic spread of the disease process is characteristically insidious, and the development of adhesions between the liver and diaphragm usually prevents the formation of generalized peritonitis.4 The same process may allow extension of the disease to the lung without pleural involvement. The anterior basilar segment of the right lower lobe is characteristically involved, due to its proximity to the dome of the diaphragm.6 However, an area of consolidation or abscess may occur within the left lower lobe if the pericardium is involved, or if an amebic hepatic abscess occurs within the left lobe of the liver. If the abscess communicates with a bronchus. a fluid level will be apparent within the lesion on the erect or decubitus examination of the chest. Hematogeneous dissemination of the disease is uncommon, but may produce an abscess within any portion of the lung, with or without an associated fluid level or pleural effusion.4

The diagnosis of pleuropulmonary amebiasis is established by the isolation of Entamoeba histolytica from the sputum, pleural fluid, or within the biopsy specimen. However, in most patients recovery of the organism is not possible and the diagnosis must be established by other parameters. Recovery of the cysts of Entamoeba histolytica within the stool provides indirect evidence as to the etiology of a suspected amebic pulmonary consolidation. However, Pande and Srivastava<sup>8</sup> were able to isolate the organism from stool specimens in only one of their 22 patients with pleuropulmonary amebiasis, and the experience of other reporters has been similar. 2,5,7 Due to the frequent association of hepatic abscess with pleuropulmonary disease, the presence of one or more filling defects within the liver scan may provide further presumptive evidence. Positive titers of antibodies

against Entamoeba histolytica may be demonstrated in some patients, but at the present time the serologic studies are not completely reliable.1,3

The treatment of pleuropulmonary amebiasis is primarily medical, but occasional patients may require surgical intervention. The drugs of choice are emetine hydrochloride and chloroquin phosphate. Emetine is administered parenterally in doses of I mg. per kg. daily for a period of 8 to 10 days. The drug is toxic to the myocardium, and electrocardiographic monitoring is required before and after each daily dose. Chloroquin is administered simultaneously in the daily dose of 0.5 gm. orally for a period of 3 weeks. Although over 90 per cent of patients will be entirely cured with proper medical therapy, occasional patients will require closed thoracotomy and drainage for resistant empyema.1,8 With judicious medical and surgical management, there are usually no permanent sequelae of the disease.

# SUMMARY

Five patients are reported with pleuropulmonary amebiasis.

The lung is the second most common extraintestinal site of amebiasis, and this complication may be seen in approximately 20 per cent of patients with amebic hepatic abscess.

The etiology of the pleuropulmonary

disease may be initially obscure, as the thoracic symptoms and signs may completely overshadow the gastrointestinal manifestations of the disease.

The judicious utilization of appropriate chemotherapeutic agents will produce a high percentage of complete cures.

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The author would like to express appreciation to George E. Lipscomb, M.D., of the Columbus Medical Center for his kind permission to include the data from Case 1 in this report.

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# MULTIPLE AMYLOID TUMORS OF THE LUNG\*

# A CASE REPORT

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AMYLOID tumor of the lung is a rare manifestation of primary amyloidosis wherein the amyloid is deposited in the pulmonary parenchyma in the form of single or multiple nodules. Because of its rarity and great clinico-radiologic interest, the following case is reported.

# REPORT OF A CASE

A 67 year old Negro male was admitted to another hospital in May 1964 with symptoms of acute cholecystitis. A preoperative chest roentgenogram at that time revealed multiple nodular densities in both lung fields which did not change during a 2 week observation period. A cholecystectomy was then performed. Abdominal exploration at the same time failed to show any neoplasm.

He was first seen at Francis Delafield Hospital in May 1967 with a history of progressive shortness of breath but no cough or weight loss. He had smoked 2 packages of cigarettes per day for 40 years and worked in the janitorial service at Kennedy Airport for 27 years.

Physical examination revealed decreased breath sounds and some rhonchi over both lungs. On subsequent examinations the lungs were clear. There were no other abnormal physical findings. A chest roentgenogram showed multiple nodular densities 3–5 cm. in diameter, scattered throughout both lungs (Fig. 1). On tomography there were calcifications in some of the nodules, but no cavitation (Fig. 2). Comparison with the chest roentgenogram of May 1964 revealed no change in the size or number of the pulmonary nodules during the past 3 years.

Urinalysis showed a 1+ proteinuria. Total serum proteins were 8.0 gm. per cent, 3.9 gm. albumin and 4.1 gm. globulin. Serum electrophoresis showed no spike. Complete blood cell count, nonprotein nitrogen, blood sugar, electrolytes, liver function tests and serum calcium and phosphorus were all normal. Barium enema study, upper gastrointestinal series, intra-

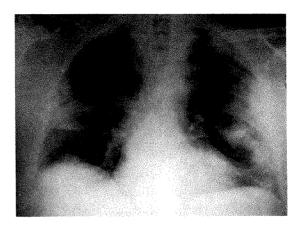


Fig. 1. Multiple nodules in the lungs, located mostly peripherally.

venous pyelography and skeletal survey showed no abnormalities. An electrocardiogram showed an A-V conduction defect. Sputum smear and culture as well as gastric juice culture were negative for acid-fast bacilli. Sputum cytology and Kveim test for sarcoid were also negative.

The patient was then considered to have a

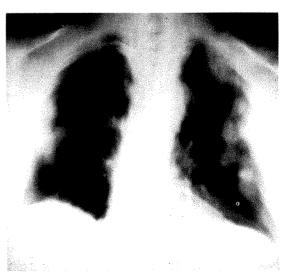


Fig. 2. Tomogram revealing calcific deposits within some nodules. The nodules are not coalescent.

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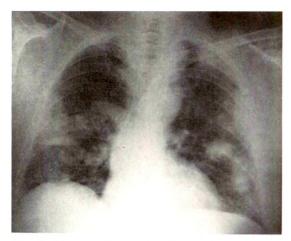


Fig. 3. Chest roentgenogram 2 years later showing some increase in the size of most of the pulmonary nodular densities.

nonprogressive, benign disease of unknown etiology and was discharged to be followed up in the clinic.

In July 1968 he developed hematuria; cystoscopy and biopsy revealed a well differentiated transitional cell carcinoma of the bladder which was treated with several instillations of thiotepa into the bladder. He was subsequently hospitalized several times for his vesical problem and underwent several cystoscopic procedures, bladder biopsies, thiotepa instillations and local radiotherapy to the neoplasm. During this period, his pulmonary status remained quiescent and his chest roentgenogram un-

changed. However, in June 1969 a follow-up chest roentgenogram showed some increase in the size of several of the pulmonary nodules (Fig. 3), and shortly thereafter the patient had an episode of hemoptysis. His pulmonary disease was investigated anew. Skin tests for fungi and a scalene lymph node biopsy were negative. Pulmonary function tests indicated a combined obstructive and restrictive ventilatory defect. An open lung and pleural biopsy was performed, and 2 nodules on the pleural surface were excised. Sections showed fibrosis. focal areas of ossification, mononuclear infiltrate and occasional giant cells. Congo red and crystal violet stains for amyloid were negative. No malignant cells were seen. A definitive diagnosis was not reached.

In October 1969 the patient was admitted again because of repeated uncontrolled gross hematuria. Bladder biopsy at this time again revealed evidence of carcinoma. It was then elected to perform a total cystectomy and ileal conduit, and he underwent surgery in December 1969. He developed severe postoperative complications and expired 8 days postoperatively.

At autopsy the lungs were found to contain numerous rock-hard masses of various sizes, the largest measuring 8 cm. in diameter (Fig. 4,  $\mathcal{A}$  and  $\mathcal{B}$ ). These were all located subpleurally but extended deeply into the parenchyma. On section these nodules showed a greenish, homogeneous, waxy center surrounded by areas of calcification and ossification. A similar type of waxy material was present within some of

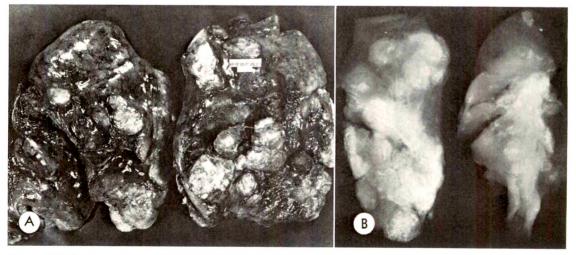


Fig. 4. (A) Gross specimen of both lungs. The noncoalescent large nodules are well shown. (B) Roentgenogram of the gross specimen. The calcification and ossification in the tumor masses are better visualized here than in the chest roentgenogram.

the hilar lymph nodes. Microscopically (Fig. 5) the nodules consisted of amorphous, acellular material, but foreign body giant cells were seen associated with some of them. The blood vessels throughout the lung parenchyma were thickened; similar thickening was present in the alveolar septa and subpleural region. Amorphous material was also found surrounding some tracheal cartilages. All these areas were positive to staining with congo red, methyl violet and thioflavin. They showed the typical changes of amyloid under the phase microscope. The larynx had numerous such nodules and the pancreas showed minute areas of positive congo red stain. No other organ was involved with amyloid. Other findings at autopsy were not relevant to this presentation.

# DISCUSSION

Reimann *et al.*<sup>16</sup> have suggested a simple clinicopathologic classification of amyloid disease which is the most widely used in the literature and is as follows:

- 1. Primary amyloidosis
- II. Secondary amyloidosis
- III. Tumor forming amyloidosis
- IV. Amyloidosis associated with multiple myeloma.

Primary amyloidosis, which has no known cause, is characterized by the absence of a coexisting chronic disease. It involves primarily the heart, muscles, skin, intestine, tongue and respiratory tract. This is usually a diffuse infiltrative process.

Secondary amyloidosis is associated with a chronic disease and involves the spleen, liver, kidneys and adrenals. 13,15,19 Primary and secondary amyloidosis are also believed to have different staining properties. However, Cohen² is of the opinion that the only distinction between the primary and secondary types of amyloidosis is the presence or absence of preceding or coexisting disease.

In secondary amyloidosis, pulmonary involvement is not frequent and, when it occurs, is usually a minor microscopic deposit, whereas in primary amyloidosis involvement of the respiratory tract occurs in 50–70 per cent of the cases<sup>2,19</sup> and to a more extensive degree.

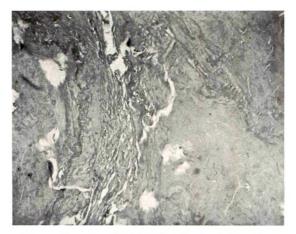


Fig. 5. Lung section showing the large deposits of amyloid. (Hematoxylin-eosin stain.)

Tumor forming amyloidosis is a special category of the primary type and is characterized by solitary or multiple tumors in the eye, bladder, urethra, pharynx, tongue and the respiratory tract. <sup>16</sup> It is usually confined to a single organ or organ system. <sup>10</sup> Amyloid tumor in the upper respiratory tract, particularly the larynx, is not uncommon, <sup>5</sup> but localization in the lung parenchyma is rare. <sup>5,10</sup>

On reviewing the literature in 1969, Hayes and Bernhardt<sup>8</sup> found 22 reported cases of multiple nodular amyloid of the lung and 7 cases of the solitary type to which they added one of their own. Later, Reeder *et al.*<sup>15</sup> reported a similar case of a single pulmonary amyloid nodule.

Prowse<sup>13</sup> divided primary amyloidosis of the respiratory tract into 3 main groups:

I. Amyloid tumor, the least common form, is single or multiple, confined to the pulmonary parenchyma and produces few, if any, symptoms.

II. Amyloid tumor involving a branch or branches of the bronchial tree. This type forms a local tumor mass which obstructs the bronchus and thus causes respiratory symptoms related to the obstruction.

III. Diffuse tracheobronchial infiltration with amyloid material deposited submucosally and causing intrinsic narrowing of the involved segment; this may go on to complete luminal obliteration with resulting

atelectasis. This is the most common group.

Our case presented predominantly as multiple amyloid tumors of the pulmonary parenchyma. At autopsy other portions of the respiratory tract were also found to be involved. The larynx was diffusely infiltrated and there were areas of submucosal tracheal infiltration as well as involvement of the alveolar septa, and the blood vessels. Thus this case appears to be a combination of Prowse's Groups I and III, the latter to a very minor degree having caused no bronchial narrowing and no clinical symptoms of obstruction.

Roentgenologically, the amyloid tumors in the lung (Prowse's Group I) can range from a few millimeters to several centimeters in diameter. The nodules are often solid, 4.6,10,15,18 but may also be cavitating. 3,8,19 Calcification is noted in about half of the reported cases, and while ossification is encountered at histologic examination, it is frequently not identified roentgenographically. The calcific deposits usually have a stippled appearance, and do not present as laminated or confluent masses. Enlargement of the hilar lymph nodes is rarely observed. Increase in the size of the nodules does occur but this is slow and minimal. 4,6,10,19

In the roentgenographic differential diagnosis of multiple large nodular densities of the lungs, a number of conditions must be considered. Most common and most important is metastatic neoplasm. Occasional cases of calcified pulmonary metastases have been reported;<sup>17</sup> the origin of these lesions may be an osteogenic sarcoma, psammomatous, papillary adenocarcinomas of the thyroid and ovary or mucoid adenocarcinoma of the colon. Therefore, once calcifications are seen in the pulmonary nodules the diagnostic possibilities of metastatic disease become restricted to the above mentioned conditions.

In the search for such calcifications, chest tomography becomes an indicated procedure in the study of multiple pulmonary nodules, similar to its use in the single pulmonary density; *i.e.*, the so-called "coin lesion."

The other possibilities in the differential diagnosis are<sup>14</sup> infarcts, fungus infection, bronchogenic tuberculosis, metastatic lung abscesses, lipoid granulomas, suppurative and gangrenous bronchopneumonia, multiple pulmonary hamartomas and echinococcal cysts. To this group must now be added multiple amyloid tumor of the lung.

Clinically it is important that in spite of the widely involved areas seen roentgenographically only few symptoms are present. These nodules are often discovered on routine roentgenography of the chest. Hemoptysis or a mild cough is occasionally encountered.

# SUMMARY

A case of multiple pulmonary amyloid tumor of the lung is reported and a short review of the literature is presented.

The condition is rare and must be included in the differential diagnosis of multiple large nodules of the lungs, particularly in instances where stippled calcifications are noted within the nodules.

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# ARTERIOGRAPHIC FINDINGS IN RENAL LYMPHOMA\*

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INVOLVEMENT of the kidneys is frequently found at autopsy in patients with malignant lymphoma. Clinical symptoms, however, are rare and when present occur late in the course of the disease. Although the clinical and urographic aspects of renal lymphoma are well documented, the arteriographic appearance only recently has received attention.

This report presents the arteriographic findings in 2 patients with lymphoma involving the kidneys.

# REPORT OF CASES

Case I. A 55 year old white female presented with a 5 month history of fullness and vague discomfort in the left abdomen in November 1969. On physical examination a tender, hard mass extended from the left flank into the left hypochondrium. Complete blood cell count and urinalysis were normal. The blood urea nitrogen was 51 mg. per cent and the serum creatinine was 1.4 mg. per cent. At the time of hysterectomy (1963), barium enema examination and intravenous urography were normal.

A roentgenogram of the chest was normal. An intravenous urogram showed a large, lobulated mass partially obliterating the left psoas shadow, a nonfunctioning left kidney, and a normal right kidney. Barium studies of the gastrointestinal tract demonstrated displacement of adjacent stomach, small bowel, and left colon by the mass. The descending colon was adherent to the mass and its mucosa was edematous.

Selective left renal arteriography demonstrated a 12×12 cm. mass elevating the left main renal artery (Fig. 1A). A rim of compressed parenchyma was present at the superior aspect of the kidney. The remainder of the kidney was replaced by the mass which stretched the adjacent intrarenal arteries. A portion of the mass was supplied by a small collection of

pathologic vessels (neovascularity), derived from an inferior capsular branch of the renal artery (Fig. 1A). Studies during the venous phase showed elevation and narrowing of the renal vein; no collateral venous channels were seen (Fig. 1B). A selective right renal arteriogram was normal.

At laparotomy a large, left retroperitoneal mass extended from the diaphragm to the iliac fossa. The descending colon was adherent to the mass with dilatation of colonic serosal vessels. Biopsies of the retroperitoneal mass and enlarged lymph nodes showed malignant lymphoma, mixed histiocytic-lymphocytic variety, which invaded the kidney grossly and microscopically.

Case II. An 18 year old white male developed nodular sclerosing Hodgkin's disease, involving the cervical, supraclavicular, axillary, and mediastinal lymph nodes in 1965. An intravenous urogram, inferior venacavagram, and lymphangiogram were normal. Exploratory laparotomy for staging revealed histologically normal periaortic and mesenteric lymph nodes and normal needle biopsy of the liver. The removed spleen contained microscopic Hodgkin's disease. The patient received megavoltage irradiation, 4,000 to 4,800 rads, to the cervical, supraclavicular, axillary, mediastinal, periaortic, iliac, and the inguinal lymph nodes.

After  $4\frac{1}{2}$  years of clinical remission, he developed pain and weakness in his right leg. There were no urinary tract symptoms. Physical examination was normal except for right leg weakness without sensory deficit. Routine laboratory work including urinalysis and blood urea nitrogen was normal except for serum uric acid of 8.8 mg. per cent and a serum lactase dehydrogenase of 330 units. Lumbar puncture was normal with negative cytology. A chest roentgenogram showed right hilar and mediastinal lymphadenopathy, which in retrospect was present 3 months earlier. A lumbar myelogram was normal. Intravenous urography demon-

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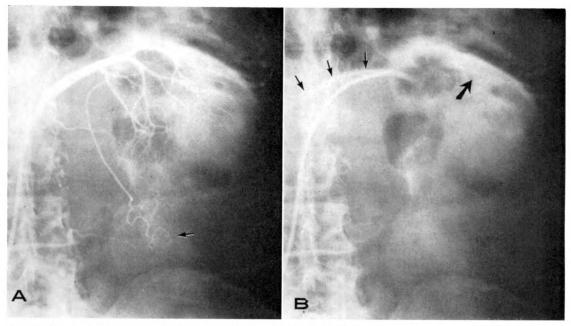


Fig. 1. Case 1. Selective left renal arteriography. (A) Arterial phase: the renal artery is elevated by a large retroperitoneal and intrarenal mass which bows adjacent intrarenal arteries. A cluster of pathologic vessels (arrow) arising from the inferior capsular artery supplies a portion of the mass. (B) Venous phase: the renal vein (small arrows) is displaced cephalad by the mass. A residual rim of compressed renal parenchyma (large arrow) is seen.

strated a 9×12 cm. mass which indented the left renal pelvis and proximal ureter producing delayed excretion of contrast material and hydronephrosis (Fig. 2). A lymphangiogram demonstrated widespread lymphomatous involvement of the retroperitoneal lymph nodes.

At selective left renal arteriography, there was elevation of the main renal artery and its primary branches by the peripelvic mass (Fig. 3A). The mass contained an abundance of pathologic vessels which were derived from branches of the renal artery. The renal parenchyma was compressed and supplied by attenuated intrarenal arteries. During the venous phase, an extensive perirenal collateral venous network was noted (Fig. 3B). Left renal venography showed that the collateral veins were the result of marked narrowing of the left renal vein by tumor (Fig. 4, A and B). Selective right renal arteriography was normal.

Because of roentgenographic evidence of disseminated disease, the patient was treated with vincristine, prednisone, nitrogen mustard, and methylhydrazine. Follow-up roentgenograms showed complete regression of the mediastinal and hilar lymphadenopathy. Repeat intravenous urography showed decrease of the left

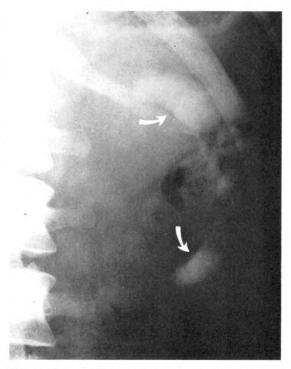


Fig. 2. Case II. An excretory urogram demonstrates a peripelvic mass causing marked hydronephrosis (arrows).

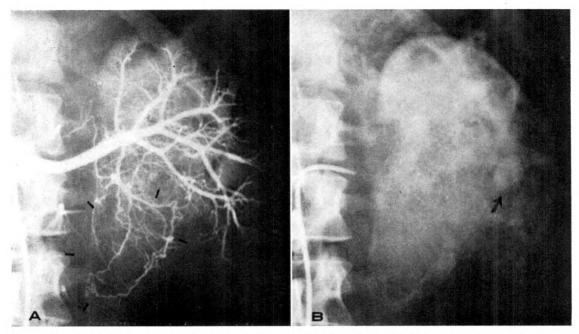


Fig. 3. Case II. Selective left renal arteriography. (A) Arterial phase: the peripelvic mass contains many pathologic vessels supplied by intrarenal arteries. (B) Venous phase: multiple perirenal collateral veins are seen. A dilated calyx (arrow) and thinned renal parenchyma are noted.

renal mass and reduction of the hydronephrosis.

# DISCUSSION

Excluding the hematopoietic system, the urinary tract is the most common site of involvement by malignant lymphoma at autopsy. In a series of 690 cases of malignant lymphoma studies at autopsy,7 233 (34 per cent) had renal involvement. Only in Hodgkin's disease was another organ, the lung, involved more often. In all the other types of lymphoma, the kidney showed the highest frequency of involvement. Other authors have reported renal involvement of from 17 to 42 per cent in cases of lymphoma at postmortem examination.<sup>2,4,5,12,14</sup> Despite this relatively high frequency, clinical manifestations are infrequent and late in appearance. Richmond et al.7 implicated the urinary tract as the major cause of death in only 2.5 per cent of their cases. Other authors also have commented on the infrequency of uremia as a terminal event.2

Renal lymphoma presents a variety of pathologic appearances including single or

multiple tumor nodules, bulky single masses, diffuse microscopic infiltration, and invasion from adjacent perirenal disease.<sup>7,12,14</sup> The roentgenographic presentation of renal lymphoma on the intravenous urogram reflects the basic pathologic form of involvement.<sup>2,7,10</sup> Diffuse enlargement of the kidneys with or without calyceal deformity, delayed excretion and hydrone-phrosis due to obstruction of the renal outflow tract, and localized pelvocalyceal and contour deformities due to nodular masses have been described.

Including our cases, 8 patients with renal lymphoma studied arteriographically have been reported. 3,4,9,15,16 There were 3 cases of Hodgkin's disease, 2 of lymphocytic lymphoma, and 1 each of histiocytic lymphoma, lymphoblastic lymphoma, and mixed histiocytic-lymphocytic lymphoma. These kidneys often had delayed or no function on intravenous urography due to obstruction of urinary drainage, with or without associated venous obstruction, and destruction of renal parenchyma. Interestingly, 1 of our cases and 3 of the previously re-

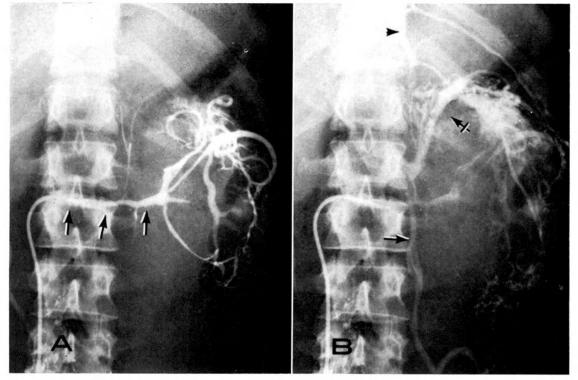


Fig. 4. Case II. Selective left renal venograms. (A) The left renal vein (arrows) and intrarenal tributaries are markedly narrowed with resultant opacification of an extensive perirenal collateral venous network. (B) Venous drainage into the hemiazygous (arrowhead), splenic (crossed arrow), and inferior mesenteric (arrow) veins is present.

ported cases3,9 were evaluated as renal papillary-tubular adenocarcinoma,13 renal masses of unknown etiology, and represented the initial clinical presentation of lymphoma in these patients.

The major arteriographic finding in most cases was stretching of the intrarenal arteries by a soft tissue mass. Most lesions demonstrated few or moderate clusters of pathologic vessels. In I case9 there was abundant neovascularity. In 2 cases collateral draining veins were observed, reflecting compromise of the renal vein (Case II; and Ref. 3).

The arteriographic appearance of renal lymphoma is not specific. In most cases it lacks the abundance of pathologic vessels that is associated with the classic renal cell carcinoma. The number and appearance of the pathologic vessels are more suggestive of other malignant or benign renal mass lesions, such as metastatic carcinoma, primary transitional cell carcinoma,6 renal

carbuncle,8 and xanthogranulomatous pyelonephritis.11

# SUMMARY

The arteriographic findings in 2 cases of lymphoma involving the kidneys are described.

The pattern of vascularity in these lesions and in the others reviewed in the literature is that of a relative paucity of pathologic vessels supplying the mass lesion. The arteriographic findings are unlike those seen in the classic hypernephroma.

Malignant lymphomas should be included in the differential diagnosis of renal masses in all patients with or without previously diagnosed lymphoma.

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# SELECTIVE HYPOGASTRIC ARTERIOGRAPHY IN UTERINE CHORIOCARCINOMA\*

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BECAUSE of characteristic great vascularity, trophoblastic malignancy is generally regarded as readily detectable by angiography. At The National Institutes of Health, pelvic angiography has been applied only to selected cases of trophoblastic malignancy. As performed by the standard method of percutaneous retrograde femoral catheterization of the lumbar aorta, the findings of pelvic angiography have sometimes been surprisingly subtle and deficient in revealing the true local extent of disease.

Three such cases are presented to document the usefulness of further study by selective hypogastric arteriography.

# REPORT OF CASES

CASE I. This 49 year old woman had a diagnosis of choriocarcinoma made by uterine curettage performed to investigate menorrhagia. At admission, 24 hour urinary gonadotropins were markedly elevated. Full evaluation for extent of disease, including full chest tomography, failed to reveal any metastatic disease. Pelvic arteriography was performed to define the limits of the neoplasm prior to total abdominal hysterectomy with bilateral salpingo-oophorectomy performed under a chemotherapy umbrella as a primary curative procedure.

With the catheter positioned 2 inches above the aortic bifurcation, a pelvic arteriogram disclosed a hypervascular uterus with dilated uterine arteries and generalized dilatation of the spiral myometrial arteries. The uterus was tipped toward the right as indicated by the course of the lateral marginal divisions of the uterine arteries (Fig. 1A). A 3.5 cm. irregular stain with a central lucency developed in the later phases of the study, superior and lateral to the marginal division of the left uterine artery (Fig. 1B). The vascular supply to the tumor stain was not demonstrated and the pos-

sibility of extrauterine disease was further investigated by a selective left hypogastric injection. Early films disclosed the tumor stain to be wholly enclosed by stretched, although clearly recognizable, spiral myometrial arteries (Fig. 1C). Later films vividly demonstrated the tumor stain (Fig. 1D).

At surgery, no extrauterine disease was found. The uterus on anatomic examination disclosed a  $2 \times 2$  cm. nodule of choriocarcinoma involving the endometrium and myometrium at the apex of the uterine fundus with no extrauterine extension (Fig. 1E).

Comment. The aortic injection disclosed a tumor stain but failed to localize it as intra or extrauterine in position. The selective study demonstrated the stain to be confined to the uterus, being wholly enclosed by spiral myometrial arteries. The tumor stain was also better demonstrated by the selective study.

CASE II. This 31 year old woman had the diagnosis of choriocarcinoma made from tissue excised from the anterior vaginal wall 2 months after spontaneous passage of a hydatidiform mole. Two uterine curettages recovered no trophoblastic tissue immediately after passage of the mole. A third curettage performed at the time the vaginal metastasis was excised was also negative for trophoblastic tissue. Upon referral to The National Institutes of Health, the 24 hour urinary gonadotropins were markedly elevated and chest roentgenograms disclosed nodular pulmonary metastases. After 3 courses of methotrexate, remission of disease was achieved with return of gonadotropins to normal levels and with the disappearance of the lung metastases as judged by whole chest tomograms. Three months later, urinary gonadotropins were again elevated. Extensive evaluation, including full chest tomograms, failed to reveal any metastatic disease. Pelvic arteriography was performed to substantiate suspected 'chemotherapy resistant" pelvic disease.

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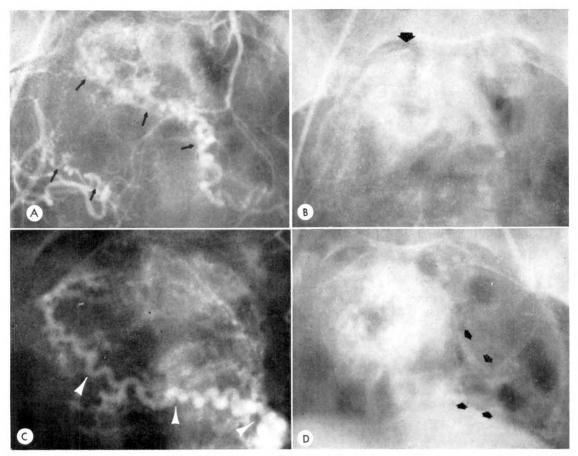


Fig. 1. Case I. (A) Aortogram, arterial phase. Best demonstration of spiral myometrial arteries from this study. The uterus is tilted toward the right as indicated by the course of the marginal divisions of the uterine arteries (arrows). A tumor stain is beginning to develop superior to the left marginal artery. (B) Aortogram, late phase. Large arrow points to a 3.5 cm. tumor stain with a central lucency. (C) Left hypogastric arteriogram, arterial phase. The spiral myometrial arteries enclosing the tumor stain are clearly shown. Arrows denote the marginal division of the left uterine artery. (D) Left hypogastric arteriogram, late phase. Vivid demonstration of tumor stain with central lucency. Arrows indicate draining uterine veins (there was no arteriovenous shunting).

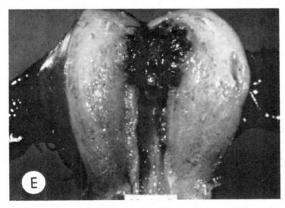


Fig. 1. (E) Operative uterine specimen. The endometrial cavity has been exposed by bivalving the anterior uterine wall. A 2.5 cm. tumor in the su-

Aortic injection demonstrated only a tiny left uterine artery and a 2 mm. diameter right uterine artery. Essentially no filling of the spiral myometrial arteries was obtained; no tumor stain was identified. The selective anterior division right hypogastric arteriogram demonstrated a faint, irregular 1.5 cm. tumor stain containing one distinct "tumor lake" medial to the lateral marginal division of the uterine artery (Fig. 2A). After 2 further courses of chemotherapy, total abdominal hysterectomy was performed. No extrauterine disease was found at surgery. Pathologic examination of

perior fundus involving endometrium and myometrium is demonstrated. the uterus disclosed a single I cm. focus of necrotic tumor confined to the myometrium (Fig. 2B).

Comment. Only the selective hypogastric arteriogram demonstrated a tumor focus. The spiral myometrial arteries were poorly filled in the selective study and not at all by the aortic injection—a finding sometimes seen after prolonged, intensive chemotherapy. The entirely intramural uterine disease in this patient was not disclosed by repeated uterine curettage performed prior to chemotherapy.

CASE III. This 34 year old woman had the diagnosis of choriocarcinoma established at thoracotomy and lobectomy for 2 right upper lobe pulmonary metastatic lesions, 6 months following a spontaneous abortion and negative uterine curettage. Upon transfer to The National Institutes of Health, she was found to have elevated urinary gonadotropins despite an initially negative pelvic examination and extensive evaluation for metastatic disease. Full chest tomograms disclosed only postlobectomy changes. She was given 4 courses of methotrexate without decrease in urinary gonadotropins. A small right adnexal mass, close to the uterus, became intermittently palpable. Six courses of actinomycin D were then given with a rapid decline in urinary gonadotropins, but not to normal levels. The right adnexal mass continued to be intermittently palpable. Pelvic arteriography was performed to define residual "chemotherapy resistant" pelvic disease.

Aortic injection revealed mildly enlarged main uterine and myometrial arteries and slow flow of contrast medium through a slightly enlarged right ovarian artery (Fig. 3A). No tumor stain was seen. Separate selective hypogastric injections demonstrated "hemiuterograms" on the side of injection. These contained small, smooth lucencies. The right hypogastric arteriogram disclosed a thin contrast stain around a I cm. central lucency in the right adnexal area, just lateral to the marginal division of the uterine artery. This was felt to represent the palpable adnexal mass (Fig. 3B). Selective left hypogastric arteriography disclosed multiple small tubo-ovarian vessels supplying a distinct left adnexal tumor stain. The ureter was deviated laterally about this tumor blush (Fig.

Hysterectomy and bilateral salpingo-oophorectomy were performed. No trophoblastic tissue was found in the uterus. Numerous pea

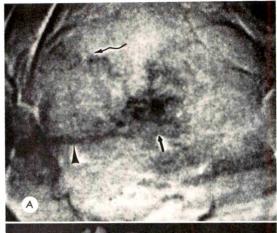




Fig. 2. Case II. (A) Subtraction film, right anterior division hypogastric arteriogram, late arterial phase. Parametrial division of the uterine artery is denoted by lower arrowhead, the tubo-ovarian arcade by upper, horizontal wavy arrow. An ill-defined 1.5 cm. uterine stain is seen containing one prominent vascular "lake" (arrow). (B) Operative uterine specimen. A section through the uterine wall discloses a I cm. necrotic intramural tumor. The endometrium is not exposed in this illustration and was not involved by tumor.

sized leiomyomata were present, probably accounting for the smooth lucencies in the otherwise normal "hemiuterograms" disclosed by the separate selective hypogastric arteriograms. The right adnexal mass proved to be an outgrowth of the right ovary and contained a hemorrhagic corpus luteal cyst. The right ovary proper contained one hemorrhagic corpus luteal cyst; the left ovary contained 2 (Fig. 3D). Trophoblastic tissue, histologically described as "an extensive decidual reaction" was found in both ovaries and about the right adnexal corpus luteal cyst.

Comment. The aortic injection failed to disclose the bilateral adnexal disease. Selective hypogastric injection revealed completely un-

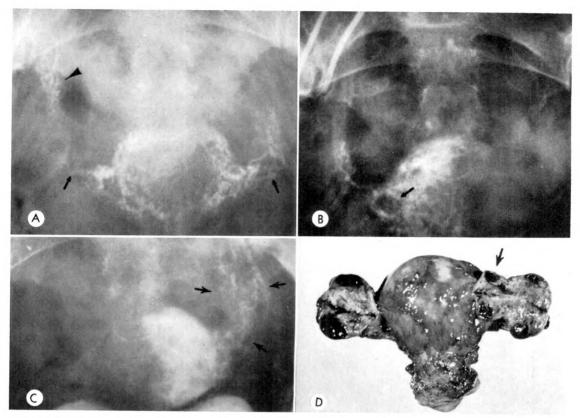


Fig. 3. Case III. (A) Aortogram, late phase. Best demonstration of adnexal vasculature from this study. No stains are seen. Bilateral single lower arrows indicate tubo-ovarian arcade vessels from the uterine arteries. Superior right arrowhead denotes prolonged opacification of terminal ramifications of the right ovarian artery. (B) Right hypogastric arteriogram, late phase. Thin contrast stain around a 1 cm. radiolucent adnexal mass (arrow). Note "hemiuterogram." (C) Left hypogastric arteriogram, late phase. Profusion of small tubo-ovarian vessels and adnexal tumor stain (enclosed by arrows). The course of the distal ureter is denoted by the 2 most lateral arrows. (D) Hysterectomy and bilateral salpingo-oophorectomy specimen, posterior view. The ovaries have been bivalved and 2 left and 1 right hemorrhagic corpus luteal cysts are present. The separate right broad ligament hemorrhagic corpus luteal cyst is denoted by an arrow. "Decidual reaction" microscopically involves both ovaries and has surrounded the right broad ligament corpus luteal cyst.

suspected left adnexal disease. Although a portion of the right adnexal disease was shown by hypogastric injection, selective ovarian ateriography may have given a more complete demonstration of disease. Corpus luteal cysts are frequently found in patients with trophoblastic malignancy. The visualization of a rim of contrast about the right adnexal cyst in this case may be due to the very unusual "decidual reaction" about it. Although mildly hypervascular, the uterus demonstrated no tumor stain or tumor "lakes" and contained no trophoblastic tissue on histologic sections.

# DISCUSSION

Pelvic angiography, as performed by percutaneous retrograde femoral catheterization of the lumbar aorta, has been liberally adopted for the investigation of trophoblastic malignancy and its high reliability in detection of disease has been stressed. (Unless otherwise specified, further discussion of angiographic findings refers to pelvic angiography as performed by this method.) Most angiographic studies have been performed prior to the institution of

systemic chemotherapy or hysterectomy in an attempt to distinguish malignancy from benign trophoblastic disease<sup>2</sup> (e.g., hydatidiform mole or missed abortion) or as a diagnostic substitute for uterine curettage in the presence of abnormal levels of urinary gonadotropins.<sup>7</sup>

In a classic monograph Borell et al.2 illustrated the often spectacular angiographic findings in 17 cases of trophoblastic malignancy (16 cases were chorioadenoma destruens) and correlated these in 15 instances with hysterectomy specimens. Three characteristic angiographic features were noted: (1) arteriovenous shunting defined as veins filling on the arterial phase of the arteriogram (it should be noted that other authors<sup>3,4</sup> have not corroborated the high frequency of arteriovenous shunting as stressed by Borell et al.); (2) small irregular contrast collections or "lakes" which, if multiple, may contribute to an inhomogeneous, irregular tumor stain; and (3) large numbers of visible intramural arteries and veins which may obscure the small contrast "lakes." The size of the tumor at hysterectomy correlated well with the extent of tumor stain; however, it was often overestimated by the extent of the unduly prominent intramural vessels.

In the largest reported series analyzing pelvic angiography in trophoblastic malignancy, Brewis and Bagshawe<sup>3</sup> noted gross angiographic changes similar to those described by Borell et al.2 in 20 patients; in only 6 was highly aggressive trophoblastic malignancy (i.e., choriocarcinoma as opposed to chorioadenoma destruens) histologically confirmed. Eight patients had only mild enlargement of normal uterine vasculature with a slight tumor blush in the later phases of the arteriographic series; in 4 a central lucency in the tumor stain was present (similar to that in Fig. 1B). Seven of these cases with more subtle arteriograms had choriocarcinoma histologically confirmed. The authors stress this association of less dramatic angiographic findings with more aggressive disease.

All reports have noted the almost invariable, nonspecific enlargement of main uterine and sometimes ovarian arteries and of the spiral myometrial vessels. Such a generalized increase in arterial vascularity as the only angiographic abnormality in a particular case constitutes inconclusive evidence for intrauterine tumor. Such an appearance is seen after the passage of a benign hydatidiform mole.<sup>2</sup> Even with known trophoblastic malignancy, such an appearance should be interpreted with caution as regression of a primary uterine lesion, either spontaneous or chemotherapy induced, in the presence of metastatic disease is well known<sup>3</sup> and is illustrated by our Case III.

A limited number of patients have been investigated by pelvic angiography before and after systemic chemotherapy. Cockshott and Hendrickse4 found with one exception that if chemotherapy had been successful, the post-treatment study will show rapid reversion of vessels to the normal appearance of a nonpregnant uterus. The exception occurs when significant arteriovenous shunting exists before treatment. Then arteriovenous fistulae may be seen after successful chemotherapy but in the absence of tumor stain. Brewis and Bagshawe3 noted decrease in abnormal circulation with favorable response to treatment, but demonstrated that abnormal circulation may remain for some time after completion of successful chemotherapy. These authors concluded that determination of the urinary gonadotropin level is a more sensitive indicator of therapeutic response. It would seem that angiographic diagnosis of viable, residual tumor after administration of chemotherapy depends on 2 criteria: (1) elevated urinary gonadotropin; and (2) demonstration of tumor "lakes" or stain.

At The National Institutes of Health, application of pelvic arteriography to malignant trophoblastic disease has been restricted to the following indications: (1) In the differential diagnosis of gestational

trophoblastic neoplasm and other tumor producing gonadotropins in the absence of histologic evidence of a prior pregnancy. Other malignancies with vastly different prognoses have been associated with elevated urinary gonadotropin levels.6 (2) To localize the extent of disease prior to contemplated hysterectomy. Especially in the older woman, hysterectomy as a curative procedure may eliminate the morbidity of prolonged chemotherapy. (3) To detect the presence and extent of residual disease in "chemotherapy resistant" cases for possible surgical intervention or intraarterial chemotherapy perfusion. Pelvic angiography as performed by lumbar aortography may yield equivocal results when used for these purposes. As illustrated by our cases, differentiation between intra and extrauterine disease may be inadequate and a tumor stain may be difficult to detect, especially after chemotherapy. As demonstrated by Altemus<sup>1</sup> for other gynecologic disorders, selective hypogastric arteriography better demonstrates spiral myometrial arteries, the tubo-ovarian vascular arcade and intra and extrauterine tumor stains. In the 3 instances reported, selective hypogastric catheterization has significantly enhanced angiographic study of trophoblastic malignancy.

# SUMMARY

Pelvic arteriography as performed by lumbar aortography often provides flagrant demonstration of trophoblastic malignancy. However, in some cases the angiographic findings may be subtle and the extent of disease, especially extrauterine, may be poorly defined.

Detection of residual pelvic disease in "chemotherapy resistant" cases has proven particularly difficult.

Three cases are presented illustrating the value of selective hypogastric arteriography in better detection and localization of pelvic trophoblastic malignancy.

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# ANGIOGRAPHY IN MASS LESIONS OF THE EXTREMITIES\*

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ANGIOGRAPHY is a preoperative technique which may be used in evaluation of masses in the extremities. Fariñas<sup>3</sup> first reported its use in 1937, and since then numerous authors<sup>1,2,4–7</sup> have attempted to determine its place in the evaluation of peripheral mass lesions.

The purpose of this paper is to relate our experience with this procedure in evaluating bone and soft tissue tumors, comment on its accuracy and usefulness, and illustrate typical and unusual cases.

## PROCEDURE

Percutaneous puncture of either a femoral or brachial artery was performed with a Kifa or Teflon needle. Rarely, a catheter was inserted by the Seldinger technique. Serial films were exposed at 1 second intervals following injection of the contrast material. The subtraction technique was applied when necessary.

## EVALUATION

Arteriography is expected to answer one or more of the following questions: "Is the mass a neoplasm?," "Is it benign or malignant?," "What is its blood supply?," and "From what part of the lesion would biopsy likely reveal the diagnosis?." In evaluating the arteriograms to answer these questions, certain signs are sought, signs which were well summarized in a paper by Strickland in 1959.6 The only pathognomonic finding is the tumor vessel which has an erratic course, lacks progressive diminution in caliber, and often ends in an area of pooling called a tumor lake (Fig. 1, A and B; and 2, A and B). Other signs which are characteristic but not diagnostic of malignancies include: abrupt ending of a normal artery

in the region of a mass; many small vessels encircling a relatively avascular area (necrotic tumor); and straightened veins coursing at right angles to the normal course of venous return. An assessment of the accuracy of these criteria will be made following a discussion of results obtained in our study. All of the lesions were eventually either biopsied or excised, allowing a histologic diagnosis to be established in each case.

## RESULTS

Of the 24 patients examined in the past 5 years, 19 were found to have neoplasms, and of these, 13 were malignant. All of the malignancies but one (a metastatic bone lesion) were sarcomas. All of the sarcomas except one were correctly identified roentgenologically, but it was possible to determine the precise tissue of origin only in the osteosarcomas. The lesion missed (Fig. 3, A and B) was a large neurofibrosarcoma in the thigh of a 69 year old woman. The roentgenologic diagnosis was benign neurofibroma. After seeing the pathologic specimen the study was re-evaluated, but even in retrospect the absence of tumor vessels, tumor stain, arteriovenous shunting, or vascular pooling did not allow the diagnosis of sarcoma. The metastatic bone lesion was thought to be an inflammatory process roentgenologically. Biopsy showed adenocarcinoma with superimposed infection (Fig. 4).

Of the 6 benign tumors, 2 were lipomas and were correctly diagnosed as such (vascular displacement around a radiolucent mass). The third was a giant cell tumor (Fig. 5, A-C) of the distal radius. Tumor vessels were thought to be present, and the lesion was termed malignant. The patho-

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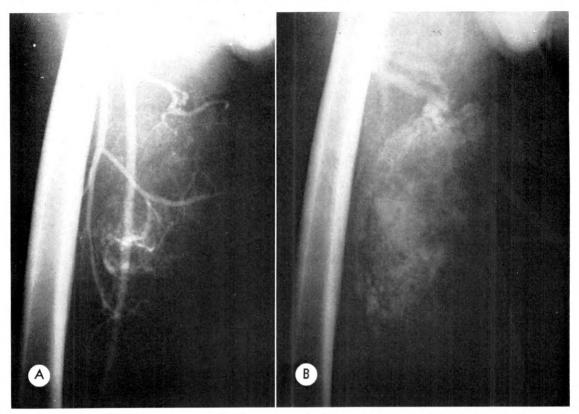


Fig. 1. (A) Numerous tumor vessels arise from the profunda femoris artery to supply a large soft tissue sarcoma in the thigh. (B) Lakes and pools of contrast material empty into large venous tributaries.

logic specimen demonstrated a Grade 2 giant cell tumor, and after 2 years the patient is well, with no evidence of local recurrence or distant spread. Three patients had hemangiomas, and although they were correctly diagnosed by arteriography, their true extent could not be determined.

Five of the patients examined did not have neoplasms. In 2 patients, a 14 year old boy and a 16 year old girl, osteomyelitis was correctly diagnosed by arteriography (vascular displacement and stretching with no tumor vessels or stain but with bone destruction and periosteal reaction). In 2 other lesions in this group (calcific bursitis and fibrous dysplasia), malignancy was excluded by arteriography. The remaining patient, a 16 year old male with a mass in the popliteal space, had a clinical history suggestive of sarcoma, and on arteriography a malignant neoplasm could not be ex-

cluded (Fig. 6, A-C). Biopsy of the lesion showed pseudosarcomatous fasciitis.

## DISCUSSION

The above data indicate a high degree of diagnostic accuracy in studying peripheral mass lesions with arteriography. In our material the questions originally posed can be answered as follows:

"Is the mass a neoplasm?"

Eighteen of the 19 neoplasms were correctly identified angiographically. One of the 5 non-neoplastic lesions was thought to be a sarcoma. The over-all accuracy of the answer to the above question is 22 of 24 or about 92 per cent.

"Is the lesion benign or malignant?"

This question was correctly answered in 21 of the 24 lesions, an accuracy of 87.5 per cent. Of the 19 patients proved histologi-

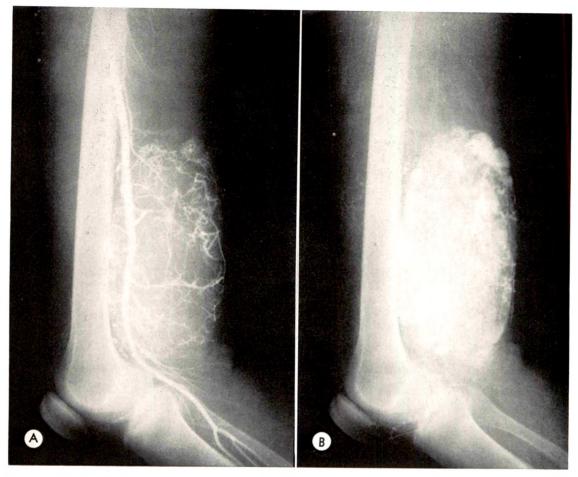


Fig. 2. (A) Hemangiopericytoma in the thigh of a young man. Tumor vessels supply the lesion. (B) Vascular puddles collect the contrast agent in the venous phase. Despite being well circumscribed, the tumor metastasized to the spine.

cally to have neoplasms, the benignity or malignancy of the lesion was correctly predicted in 17, an accuracy of about 89 per cent.

"What is the blood supply of the lesion?"

In every case the angiogram permitted accurate mapping of the arterial blood supply of the mass. This information was only occasionally valuable to the surgeon. The identification of branches from pelvic arteries supplying a tumor in the thigh was sometimes helpful in planning therapy.

"What is the ideal spot for biopsy?"

Theoretically, the more vascular parts of a nonhomogeneous lesion would be best to biopsy. In fact, the angiogram was of little practical benefit to the surgeon in choosing a biopsy site.

Obviously, arteriography was not the only source of information in these patients, and diagnostic decisions were made after consideration of several kinds of information. Since most mass lesions in the extremities proved to be sarcomas and most of them were characteristically vascular, angiography often proved to be the critical preoperative study. In several instances, an attempt to biopsy the lesion prior to arteriography had failed to yield the diagnosis. The angiogram was characteristic of a ma-

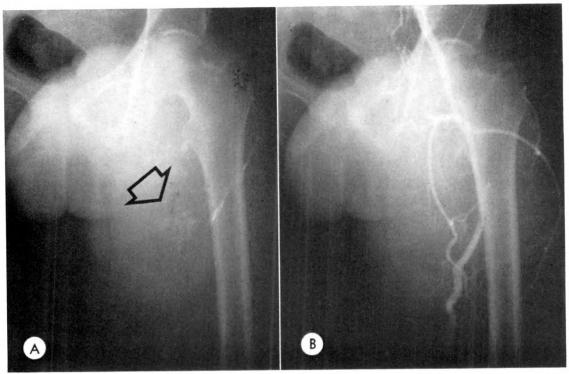


Fig. 3. (A) Sixty-nine year old woman with neurofibromatosis. Plain roentgenogram shows a large mass in the left thigh containing an irregular calcification (arrow). (B) Arteriogram shows only displacement of otherwise normal vessels. On resection, the lesion proved to be a neurofibrosarcoma.



lignant neoplasm, and excision was carried out without further delay.

# SUMMARY

Peripheral arteriography was a simple and accurate means of establishing the correct diagnosis in about 90 per cent of 24 mass lesions of the extremities. Specifically, it qualified as the diagnostic procedure of choice when a patient presented with a palpable mass in an extremity, and there were neither clinical nor plain roentgenographic findings to suggest the diagnosis.

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Fig. 4. Adenocarcinoma, metastatic to the radius. Arteriogram shows a slight increase in vascularity to the area of bone destruction, but no tumor vessels were seen. The lesion was misinterpreted as osteomyelitis

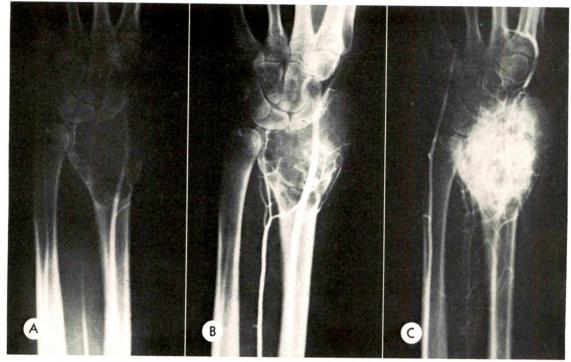


Fig. 5. (A-C) Benign giant cell tumor of the disal radius. Because of hypervascularity, the lesion was mistakenly thought to be malignant.

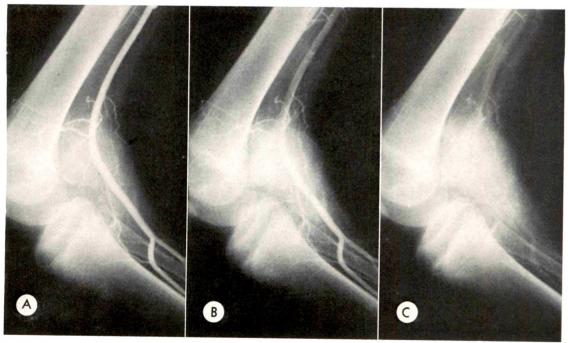


Fig. 6. (A-C) Arteriograms in a 16 year old boy with a mass in the popliteal space show a fairly well circumscribed area of hypervascularity. A sarcoma was suspected, but at operation pseudosarcomatous fasciitis was found.

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In most cases the lesion could be identified as a tumor or not, and the tumors could almost always be correctly characterized as benign or malignant. There was no morbidity from the procedure.

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# PORTOHEPATOGRAPHY WITH AN OILY CONTRAST MEDIUM\*

By FRANCESCO G. GRANONE, M.D., and GIOVANNI JULIANI, M.D. FERRARA, ITALY

GUNTZ<sup>9</sup> in a short note reported in 1967 good hepatograms following injection of I<sup>131</sup> labeled lipiodol U.F. (ultrafluid) into the spleen, but offered no details as to the technique or number of patients studied.

There have been previous reports of casual visualization of the liver in man following the injection of iodinated oil into fistulae<sup>11,12,14</sup> or during the course of lymphography.<sup>1,4,8,12,15,16</sup> Idezuki *et al.*<sup>10</sup> obtained 32 hepatograms in man after injecting lipiodol U.F. into an ileal vein; Pons *et al.*<sup>17</sup> have used 40 per cent lipiodol for portography by direct injection into the left branch of the vessel via the round ligament.

In the experimental animal, injection of a contrast medium into the spleen has been followed by portography and hepatography on several occasions, <sup>6,7,11,13</sup> and the demonstrated innocuousness of the method led to its use in man by Leger *et al.*<sup>13</sup> in 3 cases, and by Catalano<sup>3</sup> in 20 cases.

# MATERIAL AND METHOD

Portohepatography was carried out in 38 patients: 36 presented advanced metastasized gastric, intestinal, mammary and female genital cancer, or melanoma; I patient had a hydatid cyst in the liver; and I presented a right anterior costal deformity simulating such a cyst but not confirmed. The patient age ranged from 43 to 73 years. The general condition was good in 8 cases, poor in 24 and very poor in 6.

Percussion was used to determine the location of the spleen in the preanesthetized patient, who had fasted at least 5 hours. Tomography was employed for more precise localization.

Following local administration of 1 per cent novocaine, a transcutaneous splenic puncture, according to the method advised in splenoportography, was made in the medial axillary line in the 8th or 9th intercostal space. After correct positioning and the determination of pressure values, the needle was held in place by a special grip sliding over the skin to prevent shifting during the injection.

If increased endosplenic pressure was noted, a water-soluble contrast medium was injected. The presence of tributary collaterals of the vena cava was considered a contraindication to the use of the oily contrast medium and these cases are not included in this report.

Injection of the water-soluble medium, followed immediately by lipiodol U.F., was uneventful in 5 cases. The oily solution was, in all cases, preceded by the injection of 10 cm.<sup>3</sup> 0.25 per cent novocaine.

The lipiodol U.F. dose (15–20 cm.³ depending on body weight), was administered by hand in about 60 seconds. After withdrawal of the needle, hemostatics were administered in accordance with splenoportographic practice.

The first 5 roentgenograms were taken over a period of 30 seconds during the final stage of the injection. Later studies were obtained at intervals of days and weeks after the injection.

Tolerance was good in all cases: 7 cases presented with slight fever (38.5° C. maximum) which disappeared in a couple of days, as also reported by Catalano.<sup>3</sup> Iodine intolerance was not observed, even in 3 patients re-examined after 20–30 days, or in those receiving the prior water-soluble contrast medium injection.

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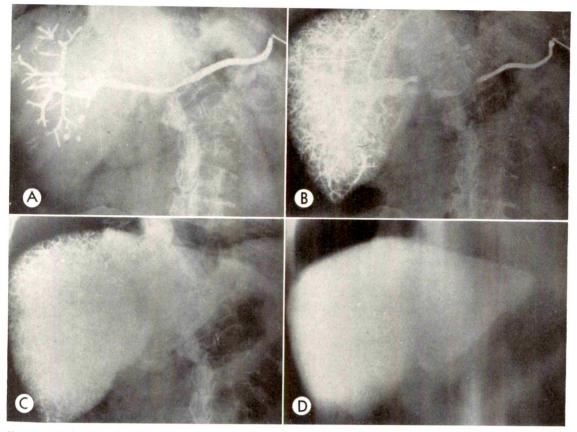


Fig. 1. (A) During the first stage, the contrast medium is shown as confluent drops on the portal vessels. (B) At the conclusion of the injection, the intrahepatic branches of the portal vein are well visualized in the right lobe, while opacification of the left lobe is incomplete. (C) After 24 hours, the whole of the liver is clearly visible. (D) Tomogram gives a particularly effective picture (absence of hepatic lesions).

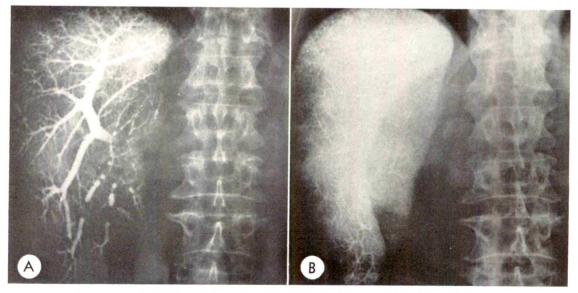


Fig. 2. (A) Normal portohepatogram. (B) In the hepatographic stage, the colon impression on the right lobe of the liver is clearly visible.

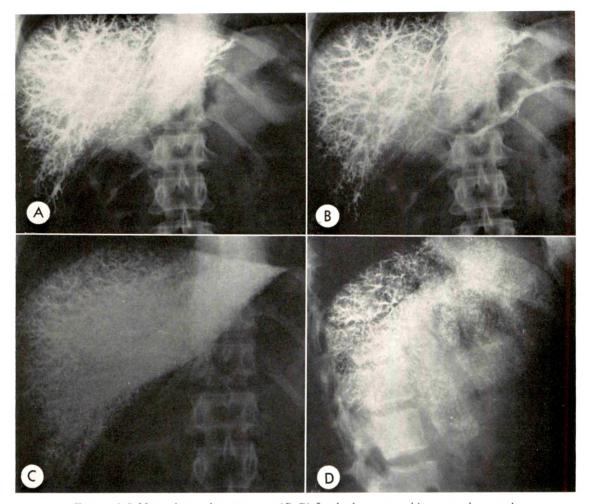


Fig. 3. (A) Normal portohepatogram. (B-D) In the hepatographic stage, the costal impressions are clearly seen in the lateral projection (D).

Two patients in the series were later successfully operated for resection of intestinal cancer 7 days after portohepatography; their roentgen findings had excluded liver metastasis, and this was confirmed at surgery. Three patients were discharged from hospital in perfect condition 24 hours after the examination.

Sero-flocculation and bromosulphalein tests in some patients before and after the injection showed no change. In some instances, opacification of the gallbladder at oral cholecystography a few days after portohepatography was found to be less intense. These findings were not collected systematically in all of the present series, however, and will not be discussed further.

## RESULTS

Early seriograms showed that single drops or emboli of the contrast medium in the splenoportal trunk, or the intrahepatic branches of the porta, later changed position with a gradual loss of edge definition until continuous opacity was reached (Fig. 1,  $\mathcal{A}$  and  $\mathcal{B}$ ). This is probably attributable to admixture with the blood as a result of lipid emulsion owing to blood alkalinity or to metabolic degradation.

For contrast and sharpness of detail, the roentgenograms of the intrahepatic portal branches were better than the already good results offered by portography with the water-soluble medium.

Visualization of the liver was particularly

intense and long-lasting and was not inferior in quality to that confluence of innumerable granular shadows interposed with residual venous images. Venous opacification was sometimes insufficient in the left lobe of the liver; the hepatographic effect was, however, good in this area despite incomplete filling of the vessels (Fig. 1, C and D). Roentgenograms of the liver became available in the hours immediately

following the injection and could be taken for as long as 10–60 days. Opacity decreased gradually, but not always homogeneously, usually from the periphery to the center of the parenchyma. Accumulation of the contrast medium in the spleen was even more persistent.

In some cases the hepatograms were so intense that the right colon (Fig. 2, A and B) and rib (Fig. 3, A–D; and 4, A–D) im-

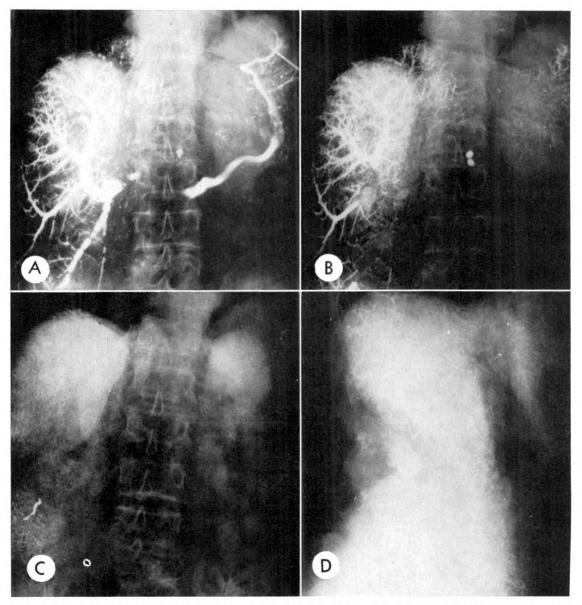


Fig. 4. (A-D) Hepatomegaly. The left lobe is clearly marked, in spite of incomplete filling of the portal branches. The costal impressions are well defined.



Fig. 5. Ptotic rotation of the liver. There is an apparent opacification defect in the right lobe, not attributable to neoplasia. (Roentgenogram taken 2 hours after the conclusion of the injection.)

pressions were visible. Delimitation of liver boundaries in hepatomegaly (Fig. 4, A-D)

and ptotic rotation (Fig. 5) were particularly effective: in the latter case, opacification was relatively poor in the right lobe, although this did not correspond with the neoplastic site discovered at surgery. This finding was attributable solely to the particular shape of the organ and to reduced parenchymal thickness (Fig. 6, A–D).

Clear opacification of the fine branches of the vena portae in conjunction with the intense hepatographic effect indicates that lacunae caused by neoplasia (Fig. 5) and small changes in the parenchyma, about 1.5 cm. in diameter, can be demonstrated; in 1 case of operated hydatid cyst, the presence of a small daughter cyst on the upper surface of the liver was revealed (Fig. 7,  $\mathcal{A}$  and  $\mathcal{B}$ ).

Complications of this procedure were negligible; in 6 cases there was a more or less copious spread of the contrast medium into the subcapsular spaces of the spleen

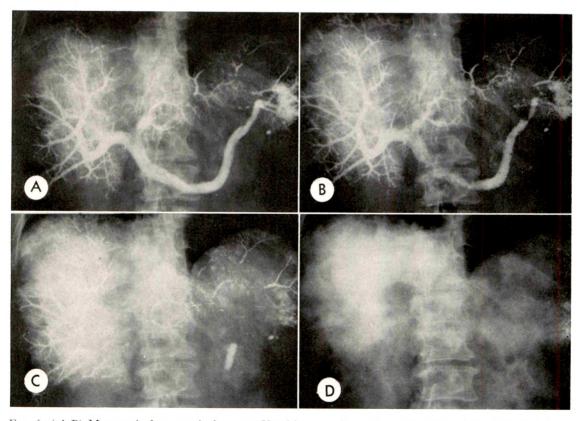


Fig. 6. (A-D) Metastasis from cervical cancer. Vasal interruption and massive, irregularly defined defects in opacification along the free margin of the right lobe and within the left lobe.

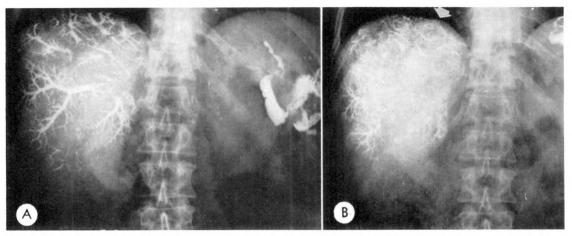


Fig. 7. (A and B) Hydatid cyst marsupialized in the right lobe near the free margin. Small daughter cyst (arrow) near upper surface (diameter 15 mm.). Spread of contrast medium to peritoneal cavity without clinically appreciable result.

and into the peritoneal cavity (Fig. 7, A and B) without noticeable subjective response. In 1 case, an appreciable quantity of the contrast material found its way into the pulmonary vessels without causing embolism or clinically demonstrable effects of any kind (Fig. 8).

## CONCLUSIONS

1. Splenoportography with an oily contrast medium was perfectly tolerated in 38 cases. Pulmonary vein embolism was found to be an unnecessary cause for concern. In

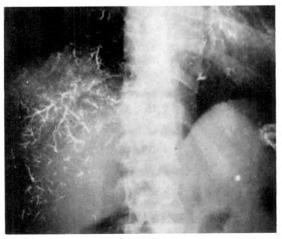


Fig. 8. Copious overflow of oily contrast medium into pulmonary vessels during portography with no clinical signs of damage.

I case there was intense opacification of the pulmonary vessels with no untoward consequences.

- 2. The examination is contraindicated in the presence of portal hypertension with florid tributary circulation from the vena cava, primarily because the roentgenograms will be no more significant than those obtained with a water-soluble medium. The literature does, in fact, contain I report of a case in which massive spread of the oily medium from the splenic vein into tributaries of the vena cava produced no serious consequences.<sup>3</sup>
- 3. Both portal and hepatic visualization are much more intense and clear than when a water-soluble medium is employed.
- 4. The examination is indicated in suspected cases of primary or secondary tumor or abscess of the liver.
- 5. A satisfactory hepatogram can be obtained of the left lobe of the liver even when opacification of the respective portal branches is incomplete.

## SUMMARY

Splenoportography was performed in 38 patients, mainly with malignant tumors and metastases, using an oily contrast medium (lipiodol U.F.). The injection was well tolerated in all cases. Visualization of the intrahepatic branches of the portal vein

was much clearer than that obtained with a water-soluble medium, and the hepatograms, in particular, were much more intense.

The examination is not recommended in the presence of portal hypertension but is otherwise indicated in the demonstration of liver tumors and abscesses.

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# THE "PSEUDOTUMOR" OF RETROPERITONEAL TUBERCULOUS LYMPHADENITIS\*

# TWO CASE REPORTS INCLUDING LYMPHANGIOGRAPHIC STUDY

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IMPROVED means of therapy have led to a significant change in the patterns of hospitalization of patients with tuberculosis. Physicians with special interests in this disease alone are becoming less common and the disease is moving away from identification as an isolated specialty. With this reorientation, the participation of the general hospital and physicians with broader interests in infectious and pulmonary diseases is increasing.

Involvement of extrapulmonary lymph nodes and osseous structures occurs as a result of post primary hematogeneous dissemination of the tubercle bacillus and presents particularly interesting diagnostic problems to the physicians involved. 5,6,8,9 Intestinal tuberculosis, as a primary source of infection, is now extremely rare in this country.9 Metastatic areas of infection usually heal without becoming clinically apparent and are familiar to the radiologist as areas of lymph node calcification in various locations of the body. Occasionally, however, one sees an immediate, or more commonly, a much delayed clinically apparent tuberculous lymphadenitis, osteomyelitis or arthritis. Cervical, axillary or inguinal lymphadenitis generally presents as palpable lymphadenopathy which is easily accessible for aspiration or biopsy to obtain material for examination and culture.

Retroperitoneal tuberculous lymphadenitis, however, presents a more difficult diagnostic problem. The incidence of extrapulmonary disease is decreasing due to more effective drug therapy, and tuberculosis may not be given serious consideration, especially when the primary pulmonary site is healed or not roentgenographically apparent. The clinical features of these infections are relatively nonspecific and the combination of abdominal masses, weight loss, anorexia and fever frequently lead to an erroneous primary diagnosis of neoplasm, especially lymphoma or carcinoma, metastatic to retroperitoneal lymph nodes.

The roentgenographic manifestations of retroperitoneal tuberculous lymphadenitis are generally indistinguishable from the lymph node enlargement of any other disease process such as lymphoma, the metastatic deposits of testicular tumors, sarcoidosis, brucellosis or various mycotic infections. The relation of the retroperitoneal lymph nodes to the kidneys, renal pelvis, ureters and the retroperitoneal portion of the duodenum is particularly important but usually nonspecific.7 Any associated involvement of the osseous structures which appears to begin in the cartilaginous portion of the skeleton and then involves adjacent osseous structures places the disease in the inflammatory

This paper will describe two such cases recently seen by us, both of which were, at first, misdiagnosed as neoplasms. It will stress the value of a careful roentgenographic search for bony lesions in these cases and the use of lymphangiography to document the extent of the lymph node disease before attempts at biopsy are made.

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## REPORT OF CASES

CASE I. This 43 year old Negro female had multiple previous admissions to the Ohio State University Hospital for the evaluation of anemia and lymphadenopathy. Pernicious anemia, thalassemia minor and hyperthyroidism had been diagnosed. Although she had had multiple lymph node biopsies on previous admissions, no specific pathology could be found. A barium enema examination 2 years prior to admission had suggested "ulcerative colitis or lymphogranuloma venereum." Four months prior to the present admission, the patient noted the onset of lower abdominal fullness and discomfort accompanied by fatigue and slight weight loss but no fever, cough, night sweats or urinary tract symptoms.

Physical examination disclosed a well developed, nervous, middle aged female in no acute distress. Moderate exophthalmos was present. There was mild left cervical and bilateral axillary and inguinal lymphadenopathy. Examination of the chest and abdomen was within normal limits. Pelvic examination disclosed an ill-defined mass in the left lateral portion of the pelvis.

Admission laboratory studies showed a normal hemoglobin and hematocrit; the white blood cell count was 15,000 with 48 per cent segmented neutrophils. Urinalysis was normal. A first strength tuberculin skin test was positive. Admission roentgenograms (Fig. 1, A and B) showed enlarged right paratracheal lymph nodes, questionable enlargement of the paraaortic and mediastinal lymph nodes and a paraspinal mass in the lower thoracic area. Intravenous pyelograms (Fig. 2, A and B) revealed medial displacement of both ureters in the pelvis and lower abdomen.

It was suggested by the referring service that the bilateral ureteral displacement was due to a previous hysterectomy in that they could feel a mass only on the left side. Bilateral lower extremity lymphangiograms were attempted to clarify the extent of the disease. Satisfactory injection was achieved on the left side only (Fig. 3). Extensive lymphadenopathy was documented in the iliac and lower paraaortic chains, and a diagnosis of Hodgkin's disease was suggested.

At surgery, multiple bilateral enlarged pelvic lymph nodes were found. Numerous biopsies were obtained which showed granulomata with central caseating necrosis. Acid fast stains showed numerous tubercle bacilli. She was immediately started on antituberculous therapy

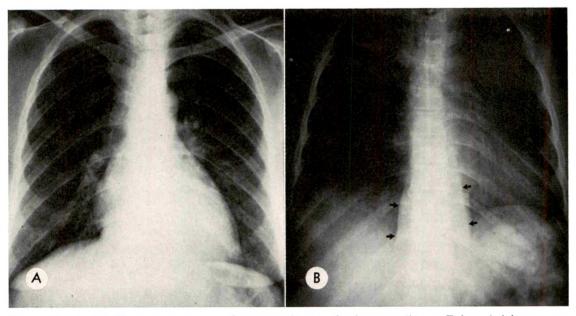


Fig. 1. Case I. (A) Chest roentgenogram shows no evidence of pulmonary disease. Enlarged right paratracheal and questionable left mediastinal lymph nodes were reported along with a questionable lower thoracic paraspinal mass. (B) Thoracic spine roentgenogram confirmed the paraspinal mass but no bone or disk destruction could be seen.

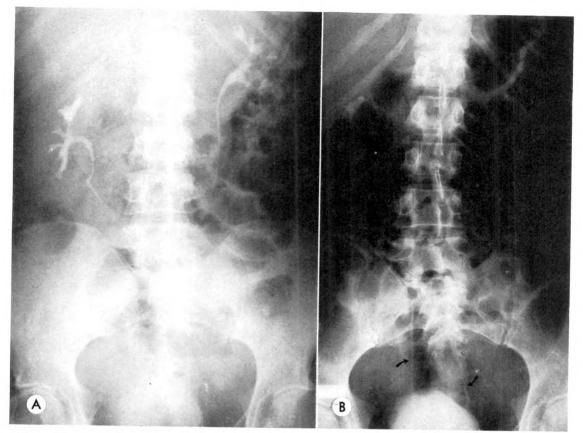
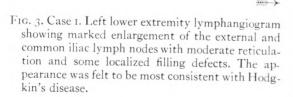


Fig. 2. Case i. (A) The kidneys and upper ureters are normal. (B) Both lower ureters are displaced medially. We have found this to be reliable evidence of pelvic lymphadenopathy.

and transferred to a tuberculosis sanatorium where she gradually improved.

Case II. This 4I year old Negro male was admitted to the Ohio State University Hospital in July, 1969 with unilateral right-sided leg edema. One month prior to admission, he first noted painless swelling of the right leg, warmth of the extremity and recurrent night sweats. He had been admitted to another hospital 6 months previously with the diagnosis of her-





niated nucleus pulposus. Following a normal lumbar myelography, he was treated with traction. However, he continued to have low back pain with radiation to the right sacral region. Past history was unremarkable except for a "kidney infection" 2 years previously and "pneumonia" I year prior to this admission.

Physical examination revealed an alert Negro male in no acute distress. Vital signs were within normal limits with the exception of an intermittent, low grade fever. Other positive physical findings were limited to the right lower quadrant of the abdomen, the right inguinal area and the right leg. A large mass which was warm, nontender and nodular in some areas was palpated in the right lower quadrant and extended into the inguinal region. The boundaries of the mass were ill-defined. The right leg was swollen from hip to foot but there was no leg tenderness.

Initial hematologic and urinary examinations were within normal limits. Serum electrolytes, blood urea nitrogen and liver function tests were also normal. A first strength tuberculin skin test was positive.

The admitting diagnosis was iliofemoral thrombophlebitis and the patient was heparinized soon after admission. Roentgenogram of the chest (Fig. 4) was normal. Intravenous urography and iliac venography documented the right pelvic mass (Fig. 5, A and B). Unilateral destruction of the right sacroiliac joint was overlooked. Right lower extremity lymphangiography (Fig. 6, A and B) showed rather marked medial displacement of the iliac vessels plus extensive enlargement of both the iliac and paraaortic lymph nodes. A diagnosis of either lymphoma or acute inflammatory disease was entertained.

Due to thephysical and roentgenographic findings of an inguinal mass, anticoagulation was discontinued, and the patient was taken to the operating room for surgical exploration of the right inguinal region and the retroperitoneal space. At surgery, the lymph nodes in the retroperitoneal space and the right suprainguinal area were found to be enlarged and tense. When the retroperitoneal space was entered for biopsy, about 500 cc. of purulent material was encountered and removed. Multiple lymph node biopsies were obtained. Histologic examination showed multiple granuloma within the lymph nodes with giant cells and occasional

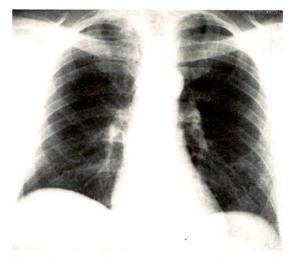


Fig. 4. Case II. Chest roentgenogram shows no evidence of active or old inflammatory disease.

areas of central caseating necrosis. Stain for acid fast bacilli was positive. The patient was placed on antituberculous therapy immediately after surgery and was discharged improved after a hospital stay of 30 days. A predischarge intravenous pyelogram (Fig. 7) had shown marked regression of the mass, partly due to the drainage but moderate regression of the lymph node enlargement had also occurred. Culture of the biopsy material revealed Mycobacterium tuberculosis hominis.

## DISCUSSION

Case I illustrates the rather protracted course which these problems may take before a large enough area of lymphadenitis or abscess develops to prompt surgical intervention and specific diagnosis. The pelvic symptoms and inflammatory changes seen on the barium enema examination 2 years before the biopsy of the pelvic lymph nodes were probably part of the initial activation of the tuberculous lymphadenitis. The paraspinal mass did not have the expected disk destruction associated with it and therefore, along with the nonspecific changes on the lymphangiogram, helped lead to an erroneous preoperative diagnosis of lymphoma. The medial displacement of ureters was very helpful in that it suggested bilateral pelvic lymphadenopathy and led to lymphangiography. We have not seen

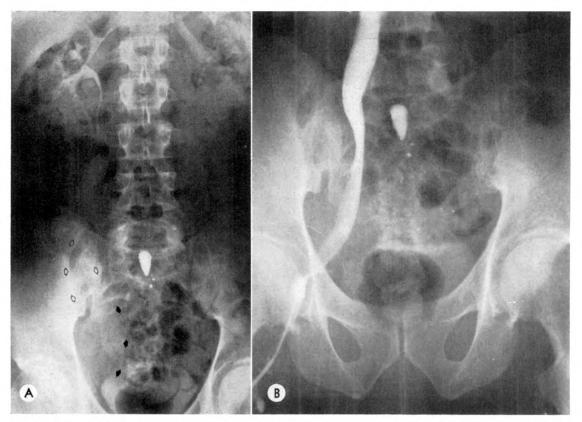


Fig. 5. Case II. (A) Intravenous urography fails to fill the distal ureter well but the soft tissue mass (solid arrows) is well seen along with extensive destruction of the right sacroiliac joint (open arrows). (B) Iliac venography reconfirms the right pelvic mass with moderate compression but no invasion of the vein.

this medial displacement of the pelvic ureters due to post-hysterectomy fibrosis as had been suggested by the referring service, and believe that such displacement invariably means lymphadenopathy. Admittedly, the normal course of the pelvic ureters is quite variable but, in this case, the medial displacement was very convincing.

Case II was suspected of being either lymphoma or infection from the lymphangiogram. The unilateral pelvic mass was, of course, well if not overly documented by physical examination, plain roentgenograms, intravenous pyelograms, inferior vena cavograms and barium enema roentgenograms. The unilateral destruction of the sacroiliac joint was probably diagnostic of osseous tuberculosis but was overlooked

both on the myelogram at another hospital and initially by us. The leg edema could have resulted from a lymphomatous mass occluding the iliac vein by extrinsic pressure, but lymph node involvement alone would not be expected to obstruct lymph flow to that extent.

There are only scattered reports of lymphangiographic studies of patients with retroperitoneal tuberculous lymphadenitis. 1,2,3,10,11 Viamonte and co-workers<sup>11</sup> published 6 cases in 1963 and compared them with cases of nonspecific infection, sarcoidosis and histoplasmosis. The more acute changes of cat scratch fever and infectious mononucleosis were also described. Three of the 6 cases had abnormal appearing lymph nodes with "marginal filling defects simulating nonspecific adenitis or

metastatic foci." Histologically, the defects could be correlated with granulomas, fibrosis and hyalinization. Sarcoidosis produced a much more granular, uniform pattern with abnormal paraaortic lymph nodes seen in 2 of 6 cases.

Albrecht et al.1 reported 20 cases of sarcoidosis and 15 cases of cervical tuberculosis which were studied by lower extremity, pelvic and abdominal lymphangiograms. Eleven of the 20 patients with sarcoid and 6 of the 15 with tuberculosis had abnormal retroperitoneal lymph nodes. Their findings were similar to those of Viamonte et al.11 with tuberculous lymph nodes showing only mild enlargement with sharply outlined filling defects, predominantly in the paraaortic area. In sarcoidosis. enlargement and "loosening of structure" predominated. Sarcoidosis could not be readily separated from lymphoma, or tuberculosis from metastatic carcinoma.

Gobbeler and Magnus<sup>3</sup> reported bilateral

lower extremity lymph edema secondary to extensive calcified tuberculous, inguinal, iliac and paraaortic lymph nodes which showed marked obstructive changes of dermal backflow and extravasation in the lower extremities but no visualization of the inguinal or retroperitoneal lymph nodes.

A very interesting case of mammary and axillary tuberculosis which was mistaken for carcinoma after upper extremity lymphangiography was recently reported by Gregl and Kienle.<sup>4</sup> They felt that an intact marginal sinus was helpful in differentiating tuberculosis from metastatic carcinoma. This would seem to be a useful observation but does not help in the additional problem of differentiating both these diseases from the lymphomas.

Our cases show a wider spectrum of lymphangiographic abnormalities than previously reported. Case I had marked enlargement of the iliac lymph nodes with both general reticulation and central filling

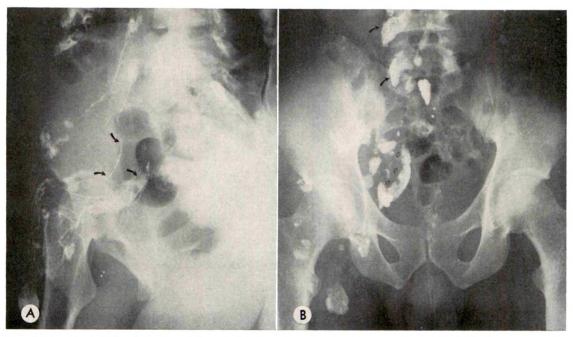


Fig. 6. Case II. (A) Postinjection oblique pelvic lymphangiogram shows marked medial displacement of the iliac vessels. (B) Twenty-four hour lymphangiogram shows both general reticulation and filling defects in grossly enlarged iliac and paraaortic lymph nodes. The majority of the mass is not accounted for by the lymph nodes, however, and at surgery there was a 500 cc. abscess.

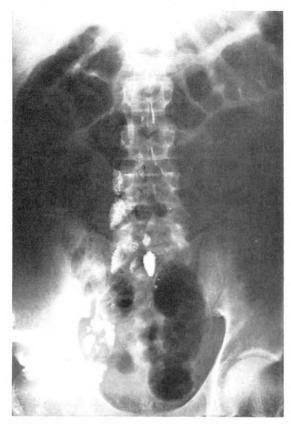


Fig. 7. Case II. Intravenous urogram 20 days after the lymphangiography shows both regression of the general lymphadenitis and the very uniform nature of the paraaortic lymph node reticulation.

defects. The appearance was more suggestive of Hodgkin's disease or sarcoidosis than the previously reported similarity to metastatic carcinoma. Case II also had strikingly enlarged lymph nodes, many of which were uniformly reticulated, suggesting lymphosarcoma, sarcoidosis or acute inflammatory disease. There was also a large mass which could not be accounted for by the contrast filled lymph nodes and apparently represented the 500 cc. abscess drained at surgery. Such a mass seen on a lymphangiogram may in future cases lead to the correct diagnosis of inflammatory disease.

## CONCLUSION

Tuberculous retroperitoneal lymphaden-

itis is easily mistaken for neoplastic disease.

Preoperative lymphangiography has shown a much wider spectrum of abnormalities in our cases than previously reported. These changes seem indistinguishable from lymphoma except for the displacement produced by abscess formation.

Lymphangiography seems very useful to demonstrate the generalized nature of the disease process and to pinpoint the easiest place for biopsy.

Identification of inflammatory spine or sacroiliac joint disease is frequently a simple and reliable clue to the correct diagnosis.

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# UNUSUAL RETENTION OF IODIZED OIL\*

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BRONCHOGRAPHY is a well established diagnostic procedure and has been performed for almost 50 years. A number of contrast agents have been tried over the years with varying success and not infrequent complications. The complications include acute allergic and febrile reactions, pulmonary insufficiency, iodism, and granuloma formation. In a Lipiodol has been blamed for aggravating tuberculosis and other inflammatory processes. Another complication, the long term retention of the contrast agent, is the subject of this report.

We recently reviewed the roentgenograms of a patient who had received visciodol for bronchography 10 years and 8 years previously. Faint traces of the contrast agent were still evident in the right middle and lower lung fields on chest roentgenograms.

## REPORT OF A CASE

A white male truck driver noted the onset of recurrent cough occasionally productive of blood-streaked sputum at the age of 29 years. In December 1960, at the age of 33 years, following an episode of brisk hemoptysis, he was referred to the University of Virginia Hospital. As part of his evaluation, bronchography, utilizing visciodol, was performed on December 28, 1960 with minimal findings suggesting early cylindric bronchiectasis in the left lower lobe. Bronchograms of the right lung were normal. Alveolarization of contrast material occurred during the procedure.

The patient continued well except for occasional blood-streaked sputum until June 1962, when he experienced another episode of severe hemoptysis. He was readmitted in July 1962 and a preliminary chest roentgenogram revealed residual visciodol bilaterally (Fig. 1). A second bronchography, again with visciodol, was carried out on July 5, 1962. The right bronchial tree again appeared normal. On the

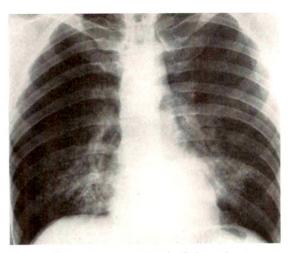


Fig. 1. Chest roentgenogram in July 1962, 2 years after the first bronchogram. Residual visciodol is quite evident bilaterally.

left there was poor filling of the bronchi of the lingular division of the left upper lobe and the superior segment of the left lower lobe. Alveolarization of visciodol again occurred (Fig. 2). Bronchoscopy demonstrated a mass in the anterior segment of the left lower lobe.

Left lower lobectomy revealed bronchitis, bronchiectasis, and inflammatory pseudopolyps.

The patient's condition since surgery has been stable. He continues to note a small amount of sputum production daily, occasionally bloodstreaked. Yearly chest roentgenograms have continued to demonstrate decreasing amounts of residual visciodol in the right lung, most recently on August 13, 1970 (Fig. 3, 4 and 5).

## DISCUSSION

Lipiodol and visciodol both contain iodized poppy seed oil as the contrast agent. Visciodol is a suspension of sulfanilamide in lipiodol. These agents are evident roentgenographically until the oil is expectorated or resorbed. The roentgenographic contrast agent in dionosil oily is propyliodon, suspended in peanut oil (arachis oil). The contrast agent is rapidly hydrolyzed and ex-

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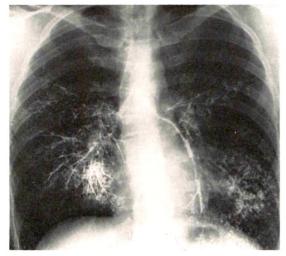


Fig. 2. Chest roentgenogram taken shortly after the second bronchogram in July 1962. Additional alveolar filling has occurred.

creted by the kidneys but the oily vehicle may be retained somewhat longer. The peanut oil is not evident roentgenographically unless it produces a pneumonitis.<sup>4</sup>

Several authors have described unusually long retention of lipiodol. Ballon and Ballon<sup>2</sup> noted that the agent is retained longer in the normal lung than in the diseased lung, in one instance up to 8 months. Amberson and Riggins<sup>1</sup> state that lipiodol may be retained for days, months or years. Wright<sup>13</sup> documented retention for I year in a patient who expired as a result of lung carcinoma. Felton<sup>5</sup> examined lung specimens from 37 patients who had bronchographies with lipiodol 3 weeks to 47 months prior to surgery. All had bronchiectasis and pneumonitis to some degree. Twenty-three specimens showed residual lipiodol up to 295 days after bronchography. The roentgenographic evidence of retention correlated well with the histologic demonstration of oil. Sheldon<sup>12</sup> reported a case of retention for 2 years in a patient who had a subacute systemic reaction to lipiodol lasting several weeks. Fortner and Miles<sup>7</sup> demonstrated an oil granuloma 6 years after bronchography with lipiodol, but the contrast agent was not evident on the roentgenogram after I year. Pentogalos and Avgoustiniatos<sup>10</sup> re-



Fig. 3. Considerable opaque medium remains in the right lung 1 year after the second bronchogram. The remaining left upper lobe showed no significant residual contrast medium.



Fig. 4. Roentgenogram of the chest taken in 1965, 3 years after bronchography, demonstrates partial clearing of the iodized oil.

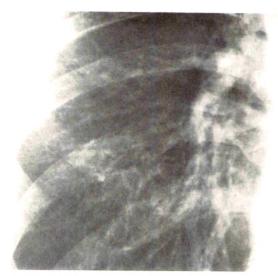


Fig. 5. Chest roentgenogram taken in August 1970 continues to demonstrate a faint residual of iodized oil, 8 years after the second bronchography.

ported a patient with bronchiectasis who retained lipiodol for I year in a collapsed middle lobe. Flamm<sup>6</sup> also reported 2 cases who received lipiodol as a treatment for asthma in whom the contrast agent was visible on roentgenography at 8 months and at I year.

Some authors have noted increased retention in abnormal lungs. Predisposing conditions have included stasis secondary to obstruction, a cavity that fills with contrast agent, or a relatively fixed lung.<sup>2,3</sup> Felton<sup>5</sup> suggested that emphysema predisposes to long retention.

The present patient represents the longest retention of iodized oil, visible on roentgenograms, that we have been able to locate in the English literature. Although this patient had mild bronchiectasis, the duration of retention was probably related to the degree of spill into alveoli in the procedures. No unusual side effects from the long retention have been noted.

## SUMMARY

A patient is reported in whom contrast medium is evident roentgenographically in the lungs 8 years following bronchography with viscoidol. The long retention appears to be related to the degree of alveolar filling. No unusual side effects have been noted.

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# LYMPHANGIOMYOMATOSIS\*

# A CLINICAL-ROENTGENOLOGIC-PATHOLOGIC SYNDROME

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In THE past 13 years, 27 cases (Table 1) have been reported of an unusual syndrome affecting the lymphatic and respiratory systems, which has been designated lymphangiomyomatosis or lymphangiomyoma by the pathologists. Although rare, these cases can be readily recognized by the combination of a very characteristic clinical picture and a typical roentgen pattern which has not previously been emphasized in the literature. We have had the opportunity to examine the roentgenograms of 7 of the cases of lymphangiomyomatosis, and here present a description

of the salient roentgenologic findings in these cases together with a brief review of the clinical and pathologic features of this distinctive syndrome.

## CLINICAL FEATURES

The sex incidence shows an overwhelming female predominance, with 26 of the 27 reported cases occurring in women. The age range is from 18 to 70 years, with most of the patients in the 30 to 50 year age group. The average age is 43 years. Most of the patients (18 of 27) presented with dyspnea, of which the most common cause

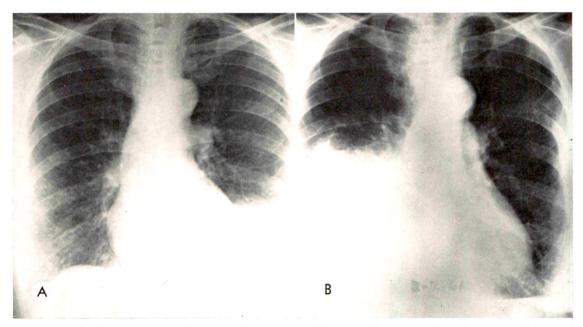


Fig. 1. Case 8. This 69 year old female developed onset of dyspnea. (A) A left chylothorax was discovered and treated with thoracentesis and subsequently by ligation of "an accessory thoracic duct." (B) Eighteen months later, a right chylothorax developed. Also note reticular changes throughout the lung fields at this time and a small right pneumothorax. Right thoracotomy and mediastinal exploration revealed a mediastinal mass which pathologically was a lymphangiomyoma. (Case courtesy of William F. Reinhoff III, M.D., Baltimore, Maryland.)

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 $\begin{tabular}{l} Table & I \\ summary of 27 reported cases \\ \end{tabular}$ 

	Care Age Son	Cumptoma	Roentge	nography	Clinical Course	Tissue*
	Case, Age, Sex	Symptoms	Effusion	Lungs	Clinical Course	Tissue
	Pachter and Lattes <sup>23</sup> 70 F Pachter and Lattes <sup>23</sup> 54 M	None Increasing dyspnea for 18 months and cyanosis of lips for 3 months	Yes, side not mentioned  None reported	Not mentioned  Bilateral pneumonic process	Tumor of thoracic duct resected. Chylous effusions controlled by small doses of roentgen irradiation. Patient alive and well, 3 years after surgery Died of "pneumonia" 3 months after first seen	Lymphangiomyoma of thoracic duct (S) Lymphangiomyoma of retroperitoneum and posterior medi- astinum. Lungs not
3.	Correll and Fischer <sup>7</sup> 47 F	Gradual onset of dyspnea	Right effusion, small posterior mediastinal mass	Bilateral reticular infiltrate not present 6 years previously	5 × 1.5 cm. mass removed from thoracic duct at surgery. Patient alive and well, 2 years later	mentioned (A)  Lymphangiomyoma of thoracic duct (S)
4.	Brewer <sup>3</sup> 41 F	Increasing dyspnea, cough, chest pain and weight loss	Left and right effusion	Normal	Thoracotomy extended to abdomen—2 nodules removed from cisterna chyli which was anastomosed to hemiazygos vein. Patient alive and well	Lymphangiomyoma of cisterna chyli (^)
5.	Maurer <sup>20</sup> 37 F	Pain right lower abdomen	Right effusion	?Infiltrate	3 years after surgery 2 cm. tumor excised from thoracic duct with ligation of duct. Patient alive and well 2 years later	Lymphangiomyoma of thoracic duct (S)
6.	Lindskog, Liebow and Glenn <sup>18</sup> 48 F	Fell down stairs and developed chest pain	Right effusion and chylous ascites	Not stated	Unknown	Lymphangiomyoma of thoracic duct (S)
7.	Lindskog, Liebow and Glenn <sup>18</sup>	No history	Not stated	Not stated but pathologic changes in lungs on photo- micrograph	Unknown	Lymphangiomyoma of the lung (S)
8.	Reinhoff, Shelley and Cornell <sup>25</sup> 69 F	Dyspnea	Left and right effusion plus pneumothorax	Diffuse reticular pattern	Two thoracotomies with talc poudrage. Removal of tissue from right side of mediastinum. Patient alive and well 18 months after surgery	Lymphangiomyoma of posterior medi- astinum and thoraci duct (S)
9.	Laipply and Sherrick <sup>17</sup> 28 F	Chronic cough and dyspnea	Left and right effusions plus pneumothorax	Fine granular mottling in the parenchyma of all lobes of both lungs	Thoracotomy with ligation of thoracic duct and decortication of the left lung. Roentgen ir- radiation (2,200 rads) to medi- astinum. Patient dead after 5 years of recurrent effusion and respiratory failure	Lymphangiomyoma of thoracic duct and mediastinal lymph nodes and of the lungs (A)
10.	Laipply and Sherrick <sup>17</sup> 50 F	Dyspnea	Left chylothorax	Uniform bilateral mottling of both lungs	Patient died following cardiac arrest during anesthesia	Lymphangiomyoma bronchopulmonary lymph nodes, thoracic duct and lung (A)
II.	Brandt and Rössing <sup>2</sup> 29 F	Dyspnea	Yes, side unknown	Diffuse mottling both lungs	Died following surgery for thoracic duct ligation	Lymphangiomyoma lymph nodes and lungs (A)
I 2.	Delarue, Depierre and Roujeau <sup>8</sup> 37 F	Dyspnea	Left effusion	Reticulonodular densities in both lungs	Died in 5 years of respiratory insufficiency	Lymphangiomyoma of thoracic duct and mediastinal lymph nodes and lungs (A)
13.	Inglis <sup>14+15</sup> 32 F	Exertional dyspnea and hemoptysis	No, but did have chylous ascites	Roentgenograms not mentioned but "pulmonary honey- combing" at autopsy	Died in 4 years of respiratory insufficiency	Lymphangiomyoma of mediastinal lymp node and lungs (A)
14	. Inglis <sup>15</sup> 31 F	Recurrent dyspnea	Right effusion and ascites	Bilateral reticular densities in lungs	Died in 4 years, cause not stated	Lymphangiomyoma in inguinal lymph node (S)
15.	. Vadas, Pare and Thurlbeck <sup>27</sup> 37 F	Dyspnea	Right effusion and pneumothorax	Diffuse parenchymal infiltrates	Died in 4 years of respiratory insufficiency	Lymphangiomyoma of abdominal, thor racic and cervical lymph nodes and lungs. Angiomyoli- poma of kidney (A)
16	Cornog and Enterline <sup>6</sup> 27 F	Dyspnea and mass in le.t retroperito- neal region	Right effusion	Diffuse linear parenchymal infiltrates	Talc poudrage and right thora- cotomy; and removal of retro- peritoneal mass on abdominal surgery. Patient died in several months of respiratory insufficiency	Lymphangiomyoma of retroperitoneal mass and in lungs or lung biopsy (S)

<sup>\*</sup> S = surgery; A = autopsy.

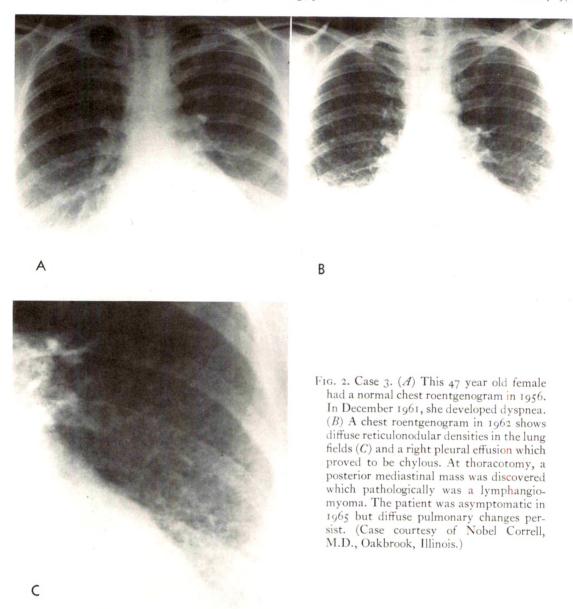
Table I (Continued)

	Case, Age, Sex	Symptoms	Roentgenography		011.1.0	
	Case, Age, Sex		Effusion	Lungs	Clinical Course	Tissue*
17.	Cornog and Enterline <sup>6</sup> 36 F	Dyspnea	Right effusion	Diffuse parenchy- mal infiltrate	Ligation of the thoracic duct. Patient died 4 months later of "interstitial pneumonia" and respiratory failure	Lymphangiomyoma of the thoracic duct and lungs (A)
τ8.	Cornog and Enterline <sup>6</sup> 56 F	Dyspnea	Bilateral effusions	Minor diffuse reticular pattern	Retroperitoneal lymphangiomyoma removed from abdomen. Subsequent effusion is controlled by several courses of roentgen therapy. Patient alive and well	Lymphangiomyoma of retroperitoneal mass (S)
19.	Cornog and Enterline <sup>6</sup> 61 F	Headaches and hypertension	No	Normal	Small paraaortic mass found incidentally at abdominal surgery. Removal resulted in complete cure	Lymphangiomyoma of retroperitoneal mass (S)
20.	Cornog and Enterline <sup>6</sup> 50 F	Abdominal pain and dyspnea	Bilateral effusions and pneumothorax	Diffuse reticular pattern	Abdominal surgery revealed retroperitoneal lymphangiomyoma which was partially removed. Patient had subsequent bilateral pleurectomies to control pleural effusions and pneumothorax. Effusions finally were controlled by nitrogen mustard. Patient alive and well, 7 years later	Lymphangiomyoma of retroperitoneal mass (S)
21.	Frack, Simon and Dawson <sup>11</sup> 40 F	Dyspnea and chest pain	Bilateral effusions with pneumothorax and chylous ascites	Diffuse retirular pattern	Lymph node biopsy revealed lymphangiomyoma. Patient sub- sequently died of renal failure and cachexia from extensive paracentesis for chylous accumulations	Lymphangiomyoma of inguinal lymph node (S)
22.	Fievez et al. <sup>10</sup> 35 F	Dyspnea	Bilateral effusions plus chylous ascites	Not stated	Patient died from "acute edema of lungs" 2 years after first effusion	Lymphangiomyoma of thoracic duct and inguinal cyst, lungs not mentioned (A)
23.	Pamukcoglu <sup>24</sup> 40 F	Dyspnea	Bilateral effusions	Diffuse reticular pattern	Patient died of respiratory failure 6½ years after first hospitalization	Lymphangiomyoma of posterior medi- astinum, retroperi- toneum and lungs (A
24.	Wuketich <sup>28</sup> 35 F	Chest pain, hemoptysis	Left effusion and pneumothorax	Diffuse reticular pattern	Patient died of cardiorespiratory failure 6 months after first effusion	Lymphangiomyoma of retroperitoneum, mediastinum and lungs (S and A)
25.	Wuketich <sup>28</sup> 41 F	Respiratory	Right effusion and recurrent bilateral pneumothorax	Diffuse reticular pattern	Nine year course ending in death	Lymphangiomyoma of mediastinum and lungs. Tuberous sclerosis of brain (A)
26.	Maurer and Koch <sup>21</sup>	Cough and chest pain	Left effusion	Small, focal infiltrate	Partial resection of lesion; living, postoperative course not described	Lymphangiomyoma of mediastinum (S)
27.	Bush <i>et al.</i> <sup>5</sup> 18 F	Chest pain	Bilateral effusion	Diffuse reticular infiltrate	Resection of retroperitoneal mass and lung biopsy. Living and well	Lymphangiomyoma of lung and retro- peritoneum (S)

<sup>\*</sup>S=surgery; A=autopsy.

was a chylous pleural effusion. Twenty-three of 27 patients developed unilateral or bilateral chylous effusions during the course of their disease, and 7 patients exhibited a pneumothorax. Four patients had chylous ascites in addition to chylous pleural effusions. Several patients gave a history of trauma immediately preceding the onset of clinical symptoms.

The disease is generally progressive with repeated episodes of chylous effusion and/or chylous ascites which may require repeated thoracenteses or paracenteses for clinical relief. In most cases surgical therapy has been attempted and has been directed towards removal of the underlying lesion (lymphangiomyoma) of the thoracic duct, or, where this has not been considered practical, towards ligation of the duct or anastomosis of the duct with the venous system. Three patients with recurrent chylothorax were treated with moderate doses of irradiation directed to the area of the thoracic duct lesion, with possible reduction in the rate of chylous accumulation. Obliteration of the pleural space by talc



poudrage or instillation of nitrogen mustard has also been attempted. Although there have been a few apparent cures after successful surgical excision of the thoracic duct lesion, and several patients have survived for long periods with recurrent disease, none of the therapeutic measures attempted has been uniformly effective.

Even when chylous effusions have been controlled or stopped by therapy, the pulmonary infiltrates, associated with the pathologic changes of "honeycomb lung," have often been progressive, leading to a respiratory death in a number of cases. Fifteen of the 27 patients reported in the literature are known to be dead, 14 of their disease.

## ROENTGENOGRAPHIC FINDINGS

The most common roentgenographic finding is pleural effusion (Fig. 1–5). Twenty-three of 27 patients exhibited pleural effu-

sion during the course of their disease, usually as a presenting feature. The effusion may be unilateral but is frequently bilateral. Thoracentesis always reveals the effusion to be chylous in nature.

Spontaneous pneumothorax was seen in 7 patients. All of the patients with pneumothorax had roentgenographic findings indicative of interstitial pulmonary disease, and 6 of the 7 had associated pleural effusions at the time of pneumothorax.

The lungs usually showed a characteristic although nonspecific pattern. Twenty of 27 patients have had findings in the lung fields. These findings are primarily a fine reticulonodular interstitial infiltrate distributed diffusely and uniformly throughout the lung fields. Kerley's lines are often present. In patients with more advanced disease, there are small cystic changes in the lung fields which give the appearance of "honeycomb" lungs. This finding is well demonstrated in the gross pathology of the lung at autopsy.

A mediastinal mass was correctly diagnosed in 2 instances, but the mediastinal and retroperitoneal masses which are a part of this disease are usually relatively small and are not demonstrable roentgenographically. Lymphangiography in 2 cases has demonstrated lymphatic block in the vicinity of the lesion<sup>21,28</sup> and, in 1 case, fistulas between paravertebral lymphatics and the pleural space.<sup>21</sup>

## PATHOLOGIC DESCRIPTION

Pathologically, lymphangiomyoma is characterized by small mediastinal or retroperitoneal tumors which usually involve the thoracic duct and consist of numerous smooth muscle bundles interspersed with anastomosing lymphatic channels (Fig. 6). In some instances, circumscribed tumor masses are not present, but there is a diffuse proliferation in the mediastinum or retroperitoneum of similarly related smooth muscle and lymphatic channels. The chylothorax, which is frequently associated with this disease, is apparently caused by devel-



Fig. 3. Case 18. This 56 year old female had an exploratory laparotomy for abdominal pain in 1952, at which time a retroperitoneal lymphangiomyoma was discovered. This was removed and the patient was treated with 1,150 rads of roentgen irradiation to the abdomen.

In 1962, the patient developed dyspnea and a chylous effusion was identified on the left. The lungs are clear. The effusion has persisted and has been controlled by thoracentesis and I course of roentgen therapy (2,300 rads). The patient's clinical course remains stable.

opment of fistulous connections between the pleural space and the chyle-bearing lymphatics of the mediastinum which are involved and probably obstructed by lymphangiomyoma. Regional lymph nodes frequently contain lymphangiomyomatous tissue, a finding which might ordinarily suggest malignancy, but no metastasis has ever been demonstrated and local organs are not invaded in a malignant fashion.

In the lungs, localized hyperplasia of smooth muscle of the pulmonary bronchioles, vessels and lymphatics is observed. When microcystic changes are present, there is widespread breakdown of normal alveolar septa. Frequently, peribronchial and perivascular lymphatics are greatly distended. These changes account for the roentgenographic findings of interstitial disease in most of the cases.

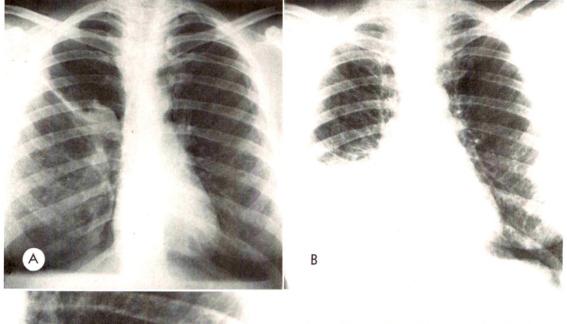




Fig. 4. Case 20. This 56 year old white female had a laparotomy in 1956 for abdominal pain at which time a retroperitoneal mass was discovered. The pathology was lymphangiomyoma. (A) In 1961, the patient developed bilateral spontaneous pneumothoraces. At this time, a diffuse linear interstitial infiltrate was identified. The patient was treated with bilateral tale poudrage. (B) In June 1964, a chylous effusion developed on the right. This was treated by thoracotomy and ligation of thoracic duct. A biopsy from the region of the ligation revealed lymphangiomyoma.

The patient subsequently developed a left pleural effusion. This effusion was treated with instillation of nitrogen mustard and the patient has had no further recurrence of effusions and remains stable. The pulmonary infiltrate present in 1964 is better seen in (C).

## DISCUSSION

Lymphangiomyoma has appeared in the literature under a variety of names—lymphangioma,<sup>20</sup> leiomyomatosis,<sup>18</sup> lymphangiomatous malformation,<sup>25</sup> intrathoracic angiomyomatous hyperplasia,<sup>17</sup> and lymphangiopericytoma.<sup>9</sup> However, the pathologic description and illustration of the

lesions in these reports leaves little doubt that they are the same, as are the clinical course and the roentgenologic findings. There are, also, a number of cases in the English language and foreign literature in which the clinical and roentgenologic findings are typical of lymphangiomyoma, but which have been excluded from this review



Fig. 5. Case 15. This 37 year old female had a history of dyspnea for 4 years and several episodes of hemoptysis. A chest roentgenogram revealed diffuse nodular infiltration in the lung fields, right pneumothorax and right pleural effusion which proved to be chylous. The patient died of respiratory insufficiency, and lymphangiomyoma was identified at autopsy in the lymph nodes and lungs. (Case courtesy of William M. Thurlbeck, M.D., Montreal, Canada.)

because of inadequate pathologic documentation<sup>4,12–14,19,22,26</sup> or because the reports are published in remote and inaccessible sources and could not be verified.<sup>1,16</sup>

Despite the paucity of well-documented reports of this disease in the literature, it is probably more common than generally realized. Three cases have appeared at the Hospital of the University of Pennsylvania in a span of 10 years. It seems likely that many cases go unrecognized or unreported.

Laipply and Sherrick<sup>17</sup> implicated trauma and proposed the following series of events: (1) rupture of thoracic duct; (2) chylomediastinum and chylothorax; (3) development of inflammation; (4) chylostasis in the mediastinum, lungs and pleura; (5) proliferation and hypertrophy of smooth muscle secondary to lymphatic obstruction; and (6) development of microcystic emphysema due to decreased interalveolar elastic tissue.

In the majority of instances, there is no good history of previous trauma and it

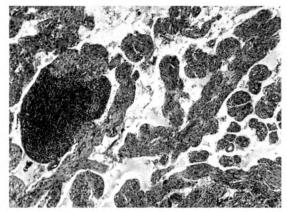


Fig. 6. Photomicrograph of lymphangiomyoma. Cords of smooth muscle cells enclose irregularly anastomosing lymphatic channels (white spaces). The endothelial lining of these channels is present but not apparent at this magnification. A focal accumulation of lymphocytes, typical of the lesion, is present at the left. (H and E, ×80.)

seems more likely that lymphangiomyoma is a lesion of developmental or hamartomatous origin rather than an unusual reaction to trauma. The presence of the disease in the lungs, lymph nodes, mediastinum and retroperitoneum suggests that this is a diffuse lesion of multifocal origin, perhaps genetically determined. Such a lesion may, of course, lead to lymphatic obstruction and rupture, so that many of the pathologic processes proposed by Laipply and Sherrick may occur as secondary and complicating effects. The lesions of lymphangiomyoma in the lungs and mediastinum bear a striking resemblance to lesions described in these locations in certain cases of tuberous sclerosis. So far, there is only one report (Table 1, Case 25) in the literature in which pathologically proven tuberous sclerosis of the brain has been associated with the pathologic lesions and clinical course of lymphangiomyoma. In the other cases of the lymphangiomyoma syndrome in which an autopsy has been performed, including an examination of the brain, evidence of tuberous sclerosis has not been found.

# SUMMARY

Lymphangiomyoma is an unusual disease, probably a congenital malformation or ham-

artoma, which is characterized by a combined proliferation of smooth muscle and lymphatic channels in the mediastinum, retroperitoneum, and regional lymph nodes, and by "honeycombing" and proliferation of smooth muscle in the lungs. Roentgenographic findings of interstitial lung disease associated with chylous pleural effusion are almost pathognomonic of this disease.

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# TUMORAL CALCINOSIS\*

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TUMORAL calcinosis is a rare entity of unknown etiology. In this condition small or large nodular calcareous masses are deposited in the soft tissues about juxta-articular areas; it occurs in young healthy subjects without calcifications in the skin, connective tissues or viscera.

Durat<sup>11</sup> in 1899 for the first time reported a case of a 17 year old girl who had calcifications in the elbow and hip; he found similar calcifications in her younger brother and called the pathologic appearance "endothelium calcifié." In 1935 Teutschländer24 used the term lipocalcino granulomatosis; he studied this lesion more than 20 years and several times changed his opinion about its etiology. In honoring his name, several authors of the European literature called the condition Teutschländer's disease. Inclan<sup>14</sup> in 1943, without reviewing the previous literature, coined the term "tumoral calcinosis" which seems more suitable, and will be used by the present authors.

## REPORT OF CASES

Case I. An 18 year old white male was admitted to Pahlavi Medical Center for the first time with the main complaint of a soft tissue mass in his left buttock of 2 years' duration. The mass was growing slowly. The general condition of the patient was excellent. There was no previous history of trauma. On physical examination there was an oval, well circumscribed nontender mass in the lateral posterior aspect of the left buttock. The overlying skin was slightly under pressure. The mass was movable, with attachment to the underlying tissues. There was no evidence of similar findings in other parts of the patient's body. The movement of both hip joints was normal.

At operation a very hard mass was removed with some difficulty. The mass measured 10×12×5 cm.; its surface was covered by yel-

lowish small nodules of various consistency measuring 2-3 mm. in size. The cut surface had a similar appearance, although there were more hard nodules than soft ones.

After a few days the patient was discharged from the hospital in good condition.

CASE II. A 38 year old white female was admitted to another hospital and was sent to us for consultation after operation. This patient complained of a hard mass in the left buttock for more than 15 years. She did not have any symptoms until 2 months ago when she experienced pain over the mass area. Gradually an abscess developed in the same area and later a fistula. A chalky material was drained from the fistula.

The patient was operated on and a hard mass measuring  $3\times6\times5$  cm. was removed with the overlying skin.

On physical examination no other mass was noted in other parts of the patient's body. Roentgenographic examination likewise revealed no evidence of other calcifications in the joint areas.

Case III. A 15 year old white male was admitted to Tadj Pahlavi Hospital with the main complaint of 2 masses, I in the left elbow and I in the right buttock. Two years previously the patient for the first time noticed a small mass in the left elbow, and a few months later he felt a similar mass in the right buttock. These masses were growing slowly but steadily. On physical examination a large very hard nontender well circumscribed mass was found in the lateral posterior aspect of the right buttock (Fig. 1). A similar mass was noted in the posterior part of the elbow joint (Fig. 2, A and B). No limitation of movement was present in the joints.

At operation both masses were removed without real difficulty. A chalk material was drained from the mass during operation. The masses from the elbow and the buttock measured  $3\times3\times4$  cm. and  $24\times19\times10$  cm., respectively.

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Fig. 1. Case III. Anteroposterior roentgenogram of the right hip reveals a large calcified mass with irregular margins. At the border of the mass there are radiolucent septa, separating the calcified areas. No ioint involvement is seen in the hip.

Case IV. A 46 year old white male was involved in an automobile accident and was admitted to the hospital. On physical examination, as an incidental finding, there was, on the lateral aspect of the right ankle joint, a hard nontender mass, measuring 4×4×3 cm. There was no similar finding in any other part of the patient's body. The mass was movable, without attachment to the bone. Roentgenographic examination of the right ankle revealed a multinodular calcified mass on the lateral aspect of the joint (Fig. 3, A and B). The calcification occupied the entire mass volume and the skin over the mass was thinner than usual. The bone and joint of the ankle showed no new or old changes. This mass has been noted by the patient for more than 15 years. At first, the mass was growing slowly and caused no symptoms: then the growth stopped altogether for several years. Consequently, he did not want to be examined by a physician.

The mass was removed completely with a small part of the skin to which it was attached.

# REVIEW OF LITERATURE

As mentioned above Durat11 in 1899 reported 2 cases, a male aged 16 years and his sister aged 17 years, who had calcified tumors and called the condition "endothelium calcifié." Teutschländer<sup>24</sup> in 1935 reported a case of a 3 year old female and named the condition as lipocalcino granulomatosis. At first he thought that spontaneous fat necrosis was the initial event,24 followed by calcium deposition and granuloma formation; in 195126 he changed his opinion and related this disease to a diencephalic hormonal regulatory defect. Ghormley et al.12 in 1941 reported a case of a boy with multiple calcified tumors, and 9 years of follow-up. Inclan14 in 1943 for the first time called this entity "tumoral calcinosis"; from then on this name was used by several authors describing similar cases. In 1958 Apak4 collected 15 cases including I case from his own clinic and reviewed the literature. He believed that the initial lesion was a deposition of cholesterol in the tendon, muscles, bursa and periosteum close to large joints, which was followed by calcification and later on necrosis and tissue granulomatosis formation. From the 15 reported cases of Apak only 1 case can be accepted as true tumoral calcinosis. Almost all authors believe now that this lesion arises from bursae. This opinion has been based on the anatomic location of the lesions; however, this theory does not explain the occurrence of a lesion where there are no bursae.7 There is some similarity between calcified bursitis and tumoral calcinosis as far as the histopathology is concerned (granulomatosis and foreign body reaction); the structure of the 2 lesions is different and the clinical and roentgenographic appearances also are quite different. The unrecognized metabolic disturbance has yet to be discovered in these patients.4,18 Harkes and Peters<sup>13</sup> are impressed by the relationship of the tumors to tendons, es-

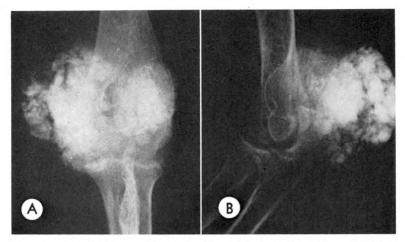


Fig. 2. Case III. (A) Anteroposterior and (B) lateral views of the left elbow. There is a multinodular calcification with no attachment to the elbow joint. Radiolucent septa are seen in the calcified mass.

pecially those without synovial sheaths. They believe that the tumor arises by proliferation of the primitive mesenchymal cell of paratenon as a result of some undetermined stimulus. In their histologic examinations they observed primitive vessels, fibrous tissue, occasional new bone trabeculae and slits which might represent primitive synovial clefts. Based on these findings,

they expressed the opinion that the origin of these tumors could be from pluripotential mesenchymal cells, which, following proliferation and maturation, produce a calcifiable matrix that is subsequently mineralized. Trauma has also been mentioned as a possible etiologic factor,<sup>21</sup> although most of the reported cases did not have any history of trauma. Parasites

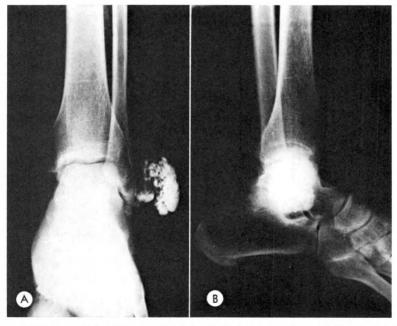


Fig. 3. Case iv. (A) Anteroposterior and (B) lateral views of the right ankle reveal a multinodular calcified mass of the lateral malleolus area. The joint is intact.

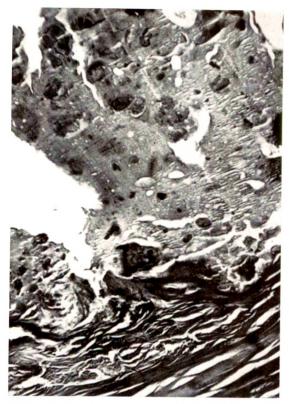


Fig. 4. Photomicrograph reveals a large area of calcification surrounded by dense fibrosclerotic tissue.

and tophi as causative agents can be discarded.

## CLINICAL FINDINGS

These tumors usually appear in the first or second decade of life. They are painless, hard, large or small mass or masses in the juxtaarticular area of the extensor surface of the joints. Their growth is slow and after months or years, according to their location, they develop into a small or large mass. Deposits about the hips may not be seen until they are 6 to 9 cm. in size, but in areas with less soft tissue can be seen when they are about 1 cm. or less in diameter. Occasionally, discomfort is noted on attempt to move the mass. The overlying skin is intact, except when secondary infection, fistulous tract or ulceration develops. No limitation of movement is present until the tumors are very large, when muscle con-

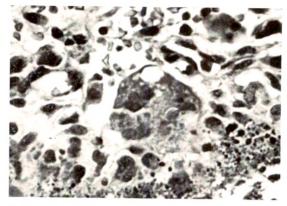


Fig. 5. In greater magnification the calcified material appears in the form of granules of different size.

traction may be observed. These patients are in good general health; however, the patient of Thomson and Tanner<sup>27</sup> died in a cachectic state from secondary amyloidosis. Harkes and Peters,13 after reviewing the literature and discarding the doubtful and misdiagnosed cases, based on the clinical, laboratory and histopathologic findings, could collect only 33 cases, including their own cases. Najjar16 in 1968 reported a case of a  $9\frac{1}{2}$  year old boy with calcinosis and pseudoxanthoma elasticum. Angioid streaks of the retina, which is a frequent finding in pseudoxanthoma elasticum, were observed in 5 previous cases of tumoral calcinosis7,14 with high phosphorus level,—a fact which raises the question of relationship of these 2 conditions. We did not observe the angioid streaks of the retina in our cases.

Of the 38 cases reported (including our own 4 cases) 16 were females and 22 were males; 13 of the 38 were from 5 families. Most of the reported cases have been in Negroes. Our 4 cases are all in white people.

The laboratory findings reveal normal serum calcium, phosphorus, blood urea and nonprotein nitrogen. Slight elevation of the serum phosphorus was noted only in 6 previous cases.<sup>7,14,17</sup>

Sometimes these tumors are seen in the older age groups, as our Cases II and IV. Careful questioning is necessary to obtain the date of onset of the lesions.

## ROENTGENOGRAPHIC FINDINGS

These tumors usually consist of calcium deposits in juxtaarticular areas and mostly on the extensor surfaces of the joints, measuring I to 30 cm. or more in longest diameter. They are dense with round or oval contour and have irregular rough borders. These masses have a multinodular appearance due to radiolucent fibrous septa separating the calcified areas from each other. This multinodular appearance is seen especially in early cases. Because of increase in the size of the tumor this pattern can gradually be obscured by overlapping calcified nodules. No bone or joint involvement has ever been noted.

The most frequent locations of these tumors are: the lateral posterior aspect of the hips (Fig. 1); the posterosuperior aspect of the elbows (Fig. 2, A and B); the lateral superior aspect of the shoulders; the posteroinferior aspect of the scapulae; the lateral aspect of the ankles (Fig. 3, A and B); the wrists and feet; the acromioclavicular joints; the metatarsal of metacarpophalangeal bones; and the fingers. Multiple tumors and lateral symmetric involvement are frequent findings.

## PATHOLOGIC FINDINGS

The tumors are firm and surrounded by a tough connective tissue giving the surface a white or pale yellowish color. The external surface is smooth in some parts and rough in others, and has a nodular appearance. The size of the tumors vary considerably according to their locations. The greatest size was of the tumor removed from the buttock in our Case III, measuring 24×19×10 cm. The largest size described in the literature was 20×19×13 cm. and the tumor weighed 3,580 grams.

When the tumor is incised, a chalky fluid containing white particles escapes; after washing the specimen, the cut surface resembles a honeycomb pattern.

The microscopic examination reveals a network of fibroblasts and collagen fibers

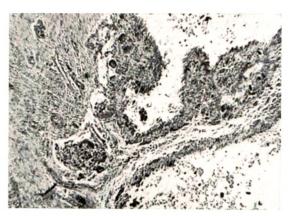


Fig. 6. There is secondary foreign body reaction around the calcified areas.

with septa extending to the surface of the mass (Fig. 4; and 5). The spaces in this network are filled with fine and coarse calcium granules. The calcium granules are surrounded by a layer of epithelioid tissue with multinucleated giant cells. Fat cells and macrophages are seen in some parts of the septa. A few plasma cells and lymphocytes are scattered throughout the section without real evidence of an inflammatory process. The lymphocytes were more numerous in our Case II (Fig. 6), which had an infected fistulous tract for the last few weeks before the operation.

No hemosiderin, bursal structure, new bone, cartilage formation or frank necrosis were noted in our cases on histopathologic examination.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis is based on the past history, clinical, roentgenologic, and especially laboratory findings. In the following diseases calcified masses could be observed: calcinosis universalis, calcinosis circumscripta, vitamin D intoxication, Burnett's syndrome, milk alkali syndrome and finally secondary hyperparathyroidism. Of all these calcifications, the ones diagnostic of tumoral calcinosis are those occurring in juxtaarticular areas in the first or second decade of life in healthy subjects, without calcification of the vessels or viscera, and

with normal blood calcium, phosphorus, and urea values.

## TREATMENT

The satisfactory treatment is complete surgical removal of the tumors. Recurrence in the same area due to incomplete removal is frequent. The recurrence could be another proof that this condition arises from mesenchymal tissue.18

Radiotherapy does not seem to be a suitable treatment for these tumors as advocated by Inclan.14

## SUMMARY

Tumoral calcinosis is a rare condition of unknown etiology. These tumors are seen in healthy subjects in the first or second decade of life. The laboratory findings for serum calcium, phosphorus, and urea are within normal limits.

Including our 4 cases from Tadi Pahlavi Hospital, 38 cases have been reported in the literature.

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## PAROSTEAL SARCOMA

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PAROSTEAL sarcoma is a rare primary malignant bone lesion, probably originating from the periosteum, and distinct from osteosarcoma. The benign appearing histologic features led earlier authors to consider it a benign tumor. Some of the names that have been applied to it are: parosteal osteoma, desmoid of bone, capsular sarcoma, periosteal chondrosarcoma, juxtacortical sarcoma, and parosteal osteogenic sarcoma. Currently, most authorities agree to call it parosteal osteosarcoma, and Aegerter believes that it should be called parosteal sarcoma, to emphasize the distinction from osteosarcoma.

Sammons *et al.*<sup>10</sup> suggest that the incidence is 0.8 per cent of all primary bone tumors and less than 4 per cent of osteogenic sarcomas; therefore, large series are difficult to obtain. Copeland and Geschickter<sup>3</sup> report 16 cases (parosteal osteoma); Dahlin,<sup>4</sup> 25 cases, (some of these are reported earlier by Dwinnell *et al.*<sup>6</sup>); Scaglietti and Calandriello,<sup>11</sup> 16 cases; Aakhus *et al.*,<sup>1</sup> 5 cases; Aegerter and Kirkpatrick,<sup>2</sup> 28 cases; and Sirsat and Doctor,<sup>12</sup> 11 cases.

This report covers 10 cases of parosteal sarcoma gleaned from 306 osteosarcomas under study at Thomas Jefferson University Hospital. All cases were reviewed by Ackerman and Spjut for confirmation of the histologic diagnosis. All patients have been followed a minimum of 3 years (Table 1).

## CLINICAL FEATURES

SEX

There were 6 females and 4 males.

AGE

In our series, the ages were 15, 19, 19, 22, 23, 28, 39, 40, 46, and 54 years. The median age was 23 years. Only 3 patients were less than 20 years of age, but 6 were less than 30 years of age.

The peak incidence occurred in the third and fourth decade, whereas the peak of osteosarcoma is in the second decade.

SITE

The site of the tumor was the distal femur in 5 patients, the proximal tibia in 3, the proximal humerus in 1, and the proximal ulna in 1. Eighty per cent of the cases occurred around the knee. The distal femur was the predominant site in all series.

All lesions involved the metaphyseal region of the long bones, with the overwhelming majority in the large bones. Sirsat and Doctor<sup>12</sup> report 7 in the femur, 3 in the humerus, and I in the tibia. Scaglietti and Calandriello<sup>11</sup> had the distal femur involved in 9 of the I4 femurs. The remaining 2 patients had lesions of the ulna and tibia.<sup>13</sup> Aegerter and Kirkpatrick<sup>2</sup> have reported 4 mandibular tumors and commented on their rarity in the flat bones.

## DURATION OF SYMPTOMS

In our series, the most common symptoms were pain and mass, present from 2 weeks to 7 years. The duration of symptoms in the 10 patients were: 2 weeks, 4 months, 5 months, 6 months, 10 months, 12 months, 12 months, and in 3, 7 years.

The duration of symptoms in other recorded series ranged from 2 months to 12

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TABLE I
SUMMARY OF IO CASES OF PAROSTEAL SARCOMA

No.	Sex	Age . at On- set (yr.)	Duration of Symp- toms	Site	Biopsy Diagnosis of Malig- nancy (after re- currence)	Treatment and Date	Results
I	F	23	7 yr.	Tibia	Ist	Block resection, Apr. 1965	Alive, Dec. 1968, 3 years
2	F	46	2 wk.	Femur	Ist	Mid thigh amputation, Feb. 1961; lobectomy, Nov. 1964; lobectomy, June 1966	Alive with disease March 1968; 7 years
3	F	19	4 mo.	Femur	зrd	Local resection, March 1956; mid thigh amputation for recur- rence, Nov. 1957	Died of unrelated dis- ease 7 years later
4	F	28	7 yr.	Femur (distal)		Excision, March 1947; recurrence excision, Jan. 1948; recurrence block resection, March 1949; recurrence and malignancy diagnosis, high thigh amputation, Feb. 1953	Alive without disease, Feb. 1968; 15 years
5	F	54	ı yr.	Femur	2nd	Mid thigh amputation, Aug. 1952; chemotherapy, Aug. 1964	Dead, May 1964
6	F	40	6 mo.	Humerus	īst	Curettement and bone graft, July 1965; recurrence four quarter amputation, May 1968	Alive without disease, Sept. 1968; 3 years
7	M	19	5 mo.	Femur	ist	Disarticulation, July 1957	Dead with disease, Sept. 1958; 14 months
8	M	15	10 mo.	Tibia	ıst	Mid thigh amputation, Aug. 1958	Alive without disease, Sept. 1968; 10 years
9	M	39	7 yr.	Ulna	īst	Local resection, Oct. 1949; recurrence, local resection and graft, Oct. 1950	Dead with disease Oct. 1953; 3 years
10	M	22	ı yr.	Tibia	ist	Mid thigh amputation, Apr. 1952	Alive without disease, Jan. 1968; 16 years

years. 12,18 Dwinnell et al.6 report a patient with symptoms for 24 years.

## BIOPSY INTERPRETATION

Of the 10 cases, in only 2 patients was the initial histologic diagnosis correct.

Osteochondroma was the first interpre- in 5 patients.

tation in 3 patients: all had local excision; and recurrence and correct diagnosis was made with the first recurrence in 1, the second recurrence in 1, and the third recurrence in the last.

Osteosarcoma was the initial diagnosis in 5 patients.

## ROENTGENOLOGIC FEATURES

The roentgenologic feature of a dense homogeneous bone mass, appearing outward from the periosteal surface, appeared in 7 out of 10 of our patients (Fig. 1–3). The margins were lobulated, and the inner portions were more dense than the periphery. The length varied from 5 to 15 cm. The smaller lesions were eccentric and the larger tumors tended to envelope the host bone.

Highly characteristic is a fine radiolucent line, which appears to separate the dense bone mass of the tumor bone from the cortex (Fig. 1). This line runs parallel to the shaft of the bone and ends at the stalk attachment of the shaft.

The smaller tumors have a smaller area of attachment to the cortex, measuring I-2 cm., but as the tumors grow the stalk also enlarges and the radiolucent line shortens. With the largest tumor, the

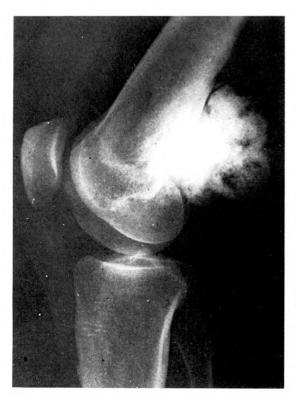


Fig. 1. Parosteal sarcoma of femur showing cleavage between tumor and host bone in a 54 year old female\_with pain for 1 year.



Fig. 2. (A and B) Parosteal sarcoma of the tibia in a 43 year old woman who had pain for 2 weeks. Single pulmonary metastases were removed 19 and 45 months after mid thigh amputation. She is alive and well 8 years after amputation.

radiolucent line, when present, is only I cm. in length at the junction of the tumor and the cortex at the extreme of the tumor margin.

The cortex is usually not disturbed and the architecture of the bone is intact. In 2 cases, there was cortical invasion of the adjacent bone. In 3 patients, the roent-genologic features were not distinctive, but appeared as stippled or homogeneous areas of new bone formation in the soft tissue, seemingly not attached to the host bone, but closely adjacent to it. The tumor may extend along the shaft 6 cm. or more. In 1 case, there was periosteal elevation extending 17 cm., and probably representing subperiosteal hemorrhage rather than neoplastic involvement.

## TREATMENT

Of the 8 patients who had amputation or disarticulation, 7 survived over 3 years,

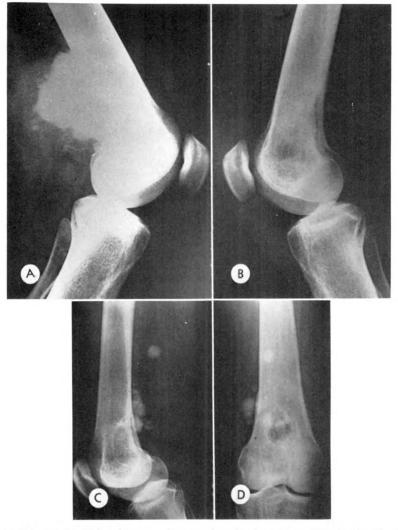


FIG. 3. A 19 year old woman with a history of 4 months of pain and swelling in the distal thigh. She was pregnant. (A) Initial appearance of the lesion reveals a large osteoblastic tumor extending into the soft tissues. Biopsy at this time was interpreted as osteosarcoma and local resection was performed. (B) Five months after local resection, recurrence is noted in the posterior soft tissues. (C and D) Eight months after the recurrence, the lesion in the soft tissues has increased in size. The osteolytic defect in the distal end of the femur is due to the previous resection. At this time, an amputation was performed, which had been delayed because of the pregnancy.

while I died with pulmonary metastasis after 14 months. One died with metastasis after 13 years, and I of a drug overdose, without evidence of residual disease, after 7 years. One is alive with metastasis after 7 years, and 4 are alive and well 3, 10, 15 and 16 years after surgery.

Of the patients who had block resection, I is alive and well after 3 years, and I, who had a local resection and bone graft, died 3 years following surgery.

Of the 10 patients, 5 are alive and well 3, 3, 10, 15, and 16 years following surgery, and 1 is alive with metastasis. One died of unrelated disease, and 3 with metastasis.

Dahlin<sup>4</sup> believes that local excision is inadequate treatment and implies the necessity of radical surgery except in very small lesions. Of the 25 patients he reported, 6 died of recurrence and metastatic disease; I died immediately after operation of unknown cause; I is lost to follow-up;

and the remaining 17 are alive and well 1, 1, 1, 1, 2, 2, 3, 3, 4, 5, 5, 6, 7, 8, 9, 10 and 18 years after surgery. Sirsat and Doctor<sup>12</sup> in 1965, reported that 7 of 11 patients were untreated and 2 survived less than 1 year, 3 less than 5 years, and 2 more than 5 years. The remaining 4 patients were treated by amputation procedures and survived 3, 5, 9, and 11 years. Wolfel and Carter<sup>13</sup> reported 3 cases alive and well 4,  $4\frac{1}{2}$  and 7 years following amputation.

## RECURRENCE AND METASTASES

Recurrence was noted in 4 patients treated initially by local excision. The recurrences appeared 9, 11, 14, and 33 months after excision. Their survivals were 85 months, 15 years, 3 years and 3 years. The 6 recurrences of the primary lesion reported by Scaglietti and Calandriello<sup>11</sup> occurred at 11, 15, 12 and 18 months, and 7\frac{3}{4} and 18 years. All but 1 of the primary lesions were treated by resection. Aakhus *et al.*\frac{1}{2} reported that 21 of the 30 primary lesions appearing in the world literature had recurred as of 1960.

Three of our patients died of pulmonary metastases, having survived 14 months, 3 years, and 13 years. Two of these patients refused any therapy for the pulmonary disease, and chemotherapy in 1 patient was ineffective. One patient had lobectomies for single pulmonary metastatic lesions occurring at 45 and 64 months, and is alive with disease after 7 years. Many writers emphasize the malignant potential of this tumor and ascribe a 25 per cent mortality to pulmonary metastasis.

## CONCLUSION

The clinical course of patients with this disease ranges from rapid death to curable. The roentgen appearance of a slow-growing, encircling osteoblastic lesion, low grade microscopic picture, or a rapidly developing recurrence should not lead to ineffectively conservative surgical methods. This entity should be treated, and ampu-

tated, if the primary tumor is anything but a very small lesion. Very small accessible lesions may be treated with block resection, but with the first recurrence, immediate amputation must be considered.

Patients treated by excision, resection, or resection and bone graft should be followed up with frequent roentgenologic examinations.

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# CHANGES IN THE STERNOCLAVICULAR JOINT FOLLOWING RADICAL NECK DISSECTION\*

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 $R^{
m ADICAL}$  neck dissection plays a major role in the management of cervical metastasis. Following the procedure, the usual consequences reported are the cosmetic effect (disfigurement), physical disability including pain in the shoulder, loss of strength and usefulness of the arm and sensory disturbances. This subject was reviewed by Ewing and Martin<sup>1</sup> who reported that 47 of the 100 patients examined noted drooping or undue prominence of the shoulder on the operated side of varying degree. They also were conscious of an unnatural "boniness" in the shoulder region and/or a deep hollow above the clavicle, as well as undue prominence of the shoulder blade (Fig. 1).

This experience coupled with the paucity of information in the literature concerning changes in the sternoclavicular joint following radical neck dissection has prompted our investigation of this problem. Knowledge of the evolution of these alterations would appear to be of clinical importance to the surgeon, radiologist and radiotherapist.

Our experience has indicated that occasionally prominence of the sternoclavicular joint may raise the issue of recurrent neoplasm. In our series, 2 patients had involvement of their sternoclavicular joint by recurrent tumor (Fig. 2,  $\mathcal{A}$  and  $\mathcal{B}$ ).

## MATERIAL AND METHOD

Our study included 58 patients who had been subjected to unilateral radical neck dissection. The period of examination varied between 3 months postoperatively to 11 years postoperatively. These patients received careful physical examinations of the shoulders and sternoclavicular joints

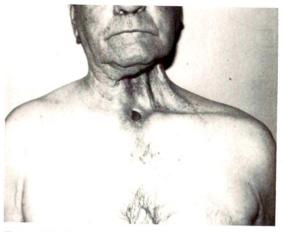


Fig. 1. Typical prominence of medial portion of the left clavicle after radical neck dissection.

and roentgenologic examinations. The roentgen examinations included chest roentgenograms, frontal laminagraphy and tangential projections of the sternoclavicular joints.

## RESULTS

In the entire group, shoulder drop was found in all cases clinically.

In most patients, a prominence of the medial end of the clavicle was noted. This prominence usually presented anteriorly and superiorly and became evident in the first few months following surgery.

In some cases, the medial end of the clavicle was less apparent than normal, suggesting posterior migration. Roentgen examinations showed joint abnormality in 24 of the 58 patients.

## ROENTGEN ASPECTS

Details of the sternoclavicular joints were demonstrated by conventional frontal laminagraphy and the tangential projection

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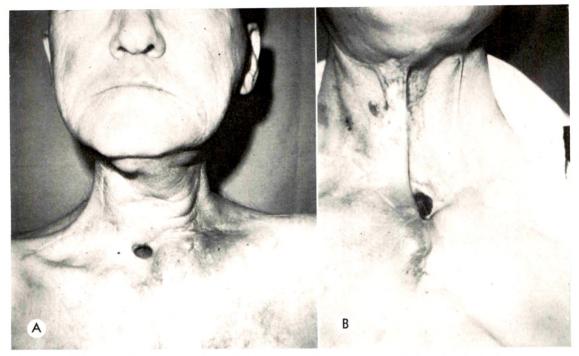


Fig. 2. (A) Recurrent epidermoid carcinoma of upper neck and left sternoclavicular ioint. (B) Recurrent carcinoma of right sternoclavicular joint.

recently described by Hobbs.<sup>2</sup> The latter view utilizes the relatively dense dorsal and ventral cortices of the manubrium sterni as reference lines for anteroposterior displacement of either clavicle (Fig. 3).

The roentgenographic studies showed a variety of disturbances of the relationships of the medial end of the clavicle and the manubrium on the side of the operation, with evidence of torque-like rotation of the clavicle in the patients with shoulder drop and subluxations superiorly, laterally, anteriorly and posteriorly.

Figure 4 shows a patient with right

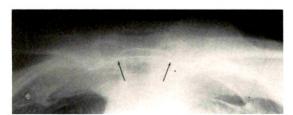


Fig. 3. Tangential projection of the sternoclavicular joints showing normal relationships in the anteroposterior plane. Arrows indicate the posterior surface of the manubrium sterni.

shoulder drop with rotation of the clavicle as demonstrated by its asymmetry in comparison with the left side. The medial end of the right clavicle has migrated superiorly, producing a discernible mass above the normal site of the sternoclavicular joint. A laminagram of this joint (Fig. 5) shows lateral subluxation of the clavicle as well.

Figure 6 illustrates another patient with anterior subluxation of the right clavicle in comparison with the left.

A laminagram in another patient (Fig. 7) indicates rotation of the right clavicle, evidenced by the asymmetric configuration of the medial end of the clavicle, and

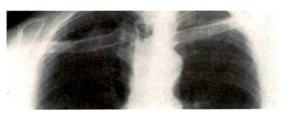


Fig. 4. Patient with right shoulder drop and rotation of the right clavicle. The medial end of the clavicle has migrated superiorly.



Fig. 5. Same patient as in Figure 4. Laminagram shows lateral subluxation of the clavicle as well.

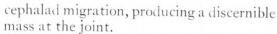


Figure 8 demonstrates the findings in a patient with a left radical neck dissection. The tangential projection shows posterior subluxation of the medial end of the left clavicle in relationship to the right.

Figure 9 shows evidence of rotation of the left clavicle as demonstrated by its asymmetry, and cephalad migration, producing a discernible mass above the joint.

## DISCUSSION

Our study indicates that significant changes occur in the sternoclavicular joint following radical neck dissection. The nature of these changes apparently has not been recognized previously, although it has long been known that many of these patients present a visible tumescence in the area of the sternoclavicular joint following surgery.



Fig. 6. Tangential projection shows anterior subluxation of the right clavicle (long arrow) as compared to left clavicle (short arrow).

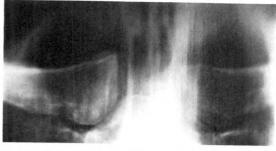


Fig. 7. Laminagram indicates rotation of the right clavicle and cephalad migration of the medial end of the right clavicle.

Roentgen analysis of the nature of this swelling indicates that it is due to alteration in the presentation of the medial end of the clavicle at the joint. The mechanism of this change is not completely clear, but obviously follows the loss of soft tissues of the neck and accompanying shoulder drop, which is a consequence of division of the spinal accessory nerve. The clavicle undergoes a torque-like rotation as well as migration of its medial end. This migration is most commonly anterior and superior, but may occasionally also be directed posterior and is often coupled with an increase in the width of the joint space, indicating lateral drift as well. In most cases the bulbous inferior aspect of the medial end of the clavicle presents anteriorly and superiorly, giving rise to the characteristic deformity illustrated in Figure 1.

It can then be stated that following radical neck dissection most patients undergo a subluxation of the medial end of the clavicle on the same side of varying degree and



Fig. 8. Tangential projection shows posterior subluxation of the left clavicle (multiple arrows) as compared to right clavicle (single arrow).



Fig. 9. Laminagram indicates rotation of the left clavicle and cephalad migration.

direction, producing the well recognized distortion of the sternoclavicular joint which follows this procedure.

On rare occasions the sternoclavicular joint may be involved with metastatic neoplasm. It is not always possible to differentiate this condition from the postoperative subluxation described here by physical examination alone. However, roentgenologic examination, particularly laminagraphic

studies, will permit this differentiation. The tangential projection is particularly useful in this regard.

#### SUMMARY

Following radical neck dissection, the medial end of the clavicle on the ipsilateral side commonly undergoes subluxation. It is this subluxation, coupled with torque-like rotation of the clavicle, which produces the characteristic deformity in the area of the sternoclavicular joint.

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# INTERNAL MAMMARY LYMPH NODE METASTASES IN BREAST CANCER: DETECTION AND MANAGEMENT\*

By PHILIP RUBIN, M.D., SUDEE BUNYAGIDJ, M.D., and COLIN POULTER, M.B., B.S. ROCHESTER, NEW YORK

NTERNAL mammary lymph node metastasis is often unrecognized when encountered clinically. Its significance has been a major point of controversy in the management of operable breast cancer among surgeons and radiation therapists.7,17,21 Despite thorough discussion in the literature, internal mammary lymph node metastasis has not been well documented: an appreciation of the development of internal mammary lymph node metastases has not been presented; the necessity of a detailed work-up is not stressed; and the best treatment policy to follow is unclear. The purpose of this presentation is to review our experience and present guidelines as to the detection and management of internal mammary lymph node metastases, referred to in the following as I.M.L.N.M.

## DISTRIBUTION OF INTERNAL MAMMARY LYMPH NODES

The internal mammary lymph node chain consists of 1 or 2 glands found in each of the 4 upper intercostal spaces along the lateral border of the sternum, lying next to the internal mammary artery and vein (Fig. 1).4 It receives afferents from the intercostal and perforating branches of the mammary lymph vessels draining the chest wall and breast. The afferents of the internal mammary artery usually join to form a single channel with the afferents of the tracheobronchial and innominate glands to the mediastinal lymph trunk. The presence of lymph nodes in the lower intercostal spaces is more variable, except for the retrosternal or lower internal mammary lymph nodes located at the xiphoidsternal-diaphragmatic junction. The first detailed anatomic study of internal mam-

mary lymph nodes was done by Stibbe (1918),19 who found an incidence of 8.5 lymph nodes on bilateral dissection. The lymph nodes were more frequent in young people than old and decreased in incidence starting with the first intercostal space. The work of Soerensen (1951)18 at postmortem studies confirmed a similar number of lymph nodes; i.e., 7.0, with distribution in the first 3 intercostal spaces. More recently, Urban, 21 in his en bloc dissection of the internal mammary lymph nodes, has found the incidence to be 91 per cent at the first intercostal space, 89 per cent at the second, 75 per cent at the third, 53 per cent at the fourth, and 13 per cent at the fifth.

These normal pathways determine the pattern of clinical presentation and spread of internal mammary lymph node metastases:

- (1) Along the manubrium or upper sternum
  - (2) At the xiphoid-sternal junction
- (3) Associated with some destruction of sternum
- (4) Mediastinal lymph node metastases. Each of these presentations, which will be discussed in more detail, dictates the diagnostic studies to be performed.

## CLINICAL PRESENTATION

In a 10 year review, from 1957 to 1967, 230 cases of breast cancer were seen in the Division of Radiation Therapy at Strong Memorial Hospital, excluding patients presenting with bone, brain or widespread metastases. Of these, 16 patients, 6.5 per cent, presented because of, or developed, internal mammary lymph node disease. Three further cases have been seen since 1967 and are included. The incidence of

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I.M.L.N.M. in this study is much less than might be anticipated from published reports, suggesting that involvement of this nodal chain for Stage I and Stage II breast cancer combined would be 25 to 35 per cent. A possible reason for the disparity between the surgical incidence and the clinical incidence may lie in the effectiveness of postoperative irradiation in controlling this problem when administered following radical or simple mastectomy.

## A. CHARACTERISTIC CLINICAL APPEARANCE OF I.M.L.N.M.

The development of a subcutaneous parasternal nodule or mass, often painless and nontender, is indicative of an internal mammary lymph node metastasis. It is usually located in the upper or lower intercostal spaces at the manubrial sternal junction or xiphoid-sternal region, respectively (Fig 2, A-C). As distinguished from skin recurrences in the operative wound, the nodule is medial to the operative scar or graft. Unlike dermal metastases, which tend to present as multiple small nodules, appearing on the chest wall and axilla and suggesting wound seeding, I.M.L.N.M. is more often an isolated finding. Its mass will often reach I to 2 cm. in diameter without infiltration of skin. Occasionally skin infiltration occurs early, and only its location suggests lymph node disease rather than dermal seeding. The involvement may be early or late in the evolution of the breast cancer process; associated mediastinal or pulmonary symptoms should suggest that the process is not superficial but results from a deeper recurrence. The majority of recurrences appeared in the first 5 years after mastectomy; the peak incidence occurred in the first year following radical mastectomy. However, 4 further cases presenting from 8 to 16 years later are noted (Fig. 3).

B. RELATIONSHIP BETWEEN SITE OF PRIMARY LESION AND LYMPH NODE INVOLVEMENT BY I.M.L.N.M.

Of the 16 cases with internal mammary lymph node metastases, 13 provided suffi-

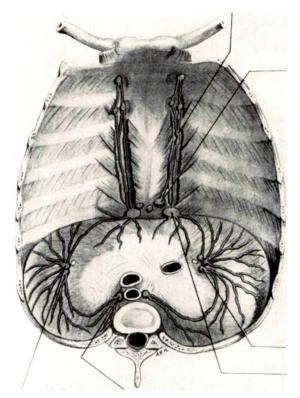
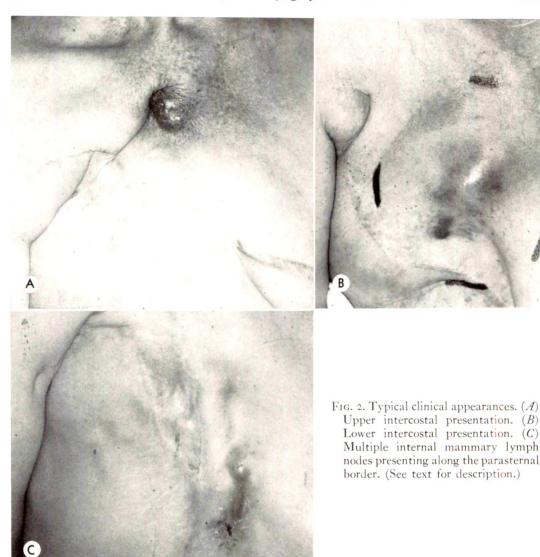


Fig. 1. The anatomy of the internal mammary lymph nodes. From Cunningham's Textbook of Anatomy, 1964.

cient information for analysis as to the original primary and lymph node disease on presentation. The majority of patients had positive axillary disease, i.e., 8 of 16 cases (50 per cent), and medial quadrant locations, i.e., 9 of 16 cases (56 per cent) (Fig. 4). Curiously, there were 3 cases of outer quadrant lesions and negative axillae with internal mammary lymph node metastases. This circumstance in Handley and Thackray's original data9 yielded an incidence of zero microscopic disease in internal mammary lymph nodes. This incidence, when compared with the information available from extended radical mastectomy series in the literature, reveals that a slightly different incidence was anticipated. Based on 2,742 cases 1,5,6,8,9,13,14,17,21,23 from 1955 to 1963, axillary involvement occurred in 75 per cent, and inner quadrant primaries in 63 per cent of cases with detectable microscopic disease in internal mammary lymph



nodes (Fig. 5). The combination of an inner quadrant primary and a positive axilla indicated that 50 per cent of such cases will have involvement of internal mammary lymph nodes. Further, an analysis of the anatomic extent of the primary lesion by TNM categories shows a correlation with the size of the primary. More T<sub>2</sub> and T<sub>3</sub> patients have internal mammary lymph node invasion and recurrence than T<sub>1</sub> patients (Table 1).

C. RELATIONSHIP OF PRIMARY TREATMENT AND I.M.L.N.M.

Radical mastectomy was performed in

14 of the 16 patients and simple mastectomy in the remaining 2. Surgery played a small role in determining the appearance of I.M.L.N.M., since these metastases were not attacked by this procedure. The role of radiation therapy was more significant. The majority of the patients with recurrence in internal mammary lymph nodes had no postoperative irradiation, *i.e.*, 11 of 16 (68 per cent) (Table II). Those who were treated by radiation therapy, in 3 of 5 instances, developed contralateral I.M.L.N.M. However, in no instance have we encountered an internal mammary lymph node recurrence in those

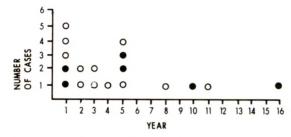


Fig. 3. Distribution of internal mammary lymph node metastases by time interval following primary surgery; also indicates relation to postoperative irradiation. ○=no postoperative radiation therapy; ●=postoperative radiation therapy.

cases treated electively with postoperative irradiation in our division. This would suggest that radiation therapy is capable of sterilizing microscopic nodal disease. Since the expected incidence is 10–30 per cent of such overt involvement, it is important to note that no cases of I.M.L.N.M. have been encountered to date. The techniques employed in our division are:

(1) Direct internal mammary fields delivering a dose of 4,500 rads in 4 to  $4\frac{1}{2}$  weeks at a depth of 3 cm., the field being 6 cm. wide, with the medial

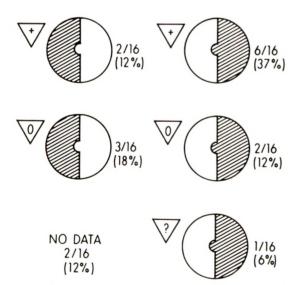


Fig. 4. Location of the primary breast lesion and axillary lymph node status at the time of initial surgery is shown in patients subsequently developing internal mammary lymph node metastases. In I case the location of the primary lesion is known but not the status of the axilla.

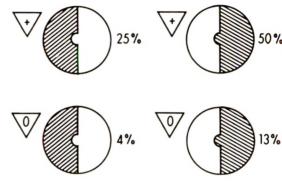


Fig. 5. Location of the primary lesion and the axillary involvement related to the internal mammary lymph node involvement is demonstrated in 2,742 cases published by 8 authors.

border in the midline, and the length being a function of the size of the patient's chest extending to the bottom of the xiphoid.

(2) McWhirter's tangential fields, where slightly higher doses are given of 5,000 rads in 5 weeks. It is essential to obtain the contour of the patient's chest and locate the ipsilateral internal mammary lymph nodes. Depending on the shape of the chest (i.e., round vs. flat) and the size, an excessive amount of lung tissue may be incorporated into the tangential fields. To avoid untoward effects, we use a direct field beyond 22 cm. field separation. It is important to place the edge of the medial tangen-

TABLE I
SIXTEEN CASES OF INTERNAL MAMMARY LYMPH NODE
METASTASES IN WHICH THE CLINICAL AND PATHOLOGIC
STAGE OF THE AXILLARY LYMPH NODES WAS KNOWN

	Axilla+	Axilla —	No Data
$T_1N_0$		2	
$T_1N_1$		I	
$T_2N_0$	2		I
$T_2N_?$	I	I	
$T_3N_0$	2		
$T_3N_1$	I		
$T_3N_2$	I		
No Data	I	I	2*

<sup>\*</sup> The 2 No Data cases had simple mastectomies.

TABLE II

PRIMARY TREATMENT IN PATIENTS DEVELOPING
INTERNAL MAMMARY LYMPH NODE METASTASES

	Post- operative Radiation Therapy	No Post- operative Radiation Therapy
Radical Mastectomy Simple Mastectomy	4 = 25% $1 = 6%$	10 = 62% $1 = 6%$

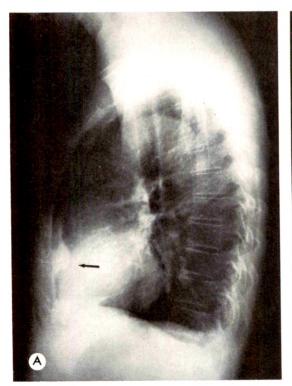
tial field on the opposite side of the midline to be certain that the ipsilateral internal mammary lymph nodes are in the field, if no direct field is used.

D. DIAGNOSTIC RADIOLOGIC FEATURES OF I.M.L.N.M.

Once a parasternal recurrence is suspected to be an I.M.L.N.M., chest roentgenograms in anteroposterior and lateral views should be obtained. Also, tomograms of the sternum are important.<sup>14</sup> Specialized pro-

cedures such as pneumomediastinum, mediastinoscopy and isotope scans are not routinely advocated but may be of interest if available. The findings of a mass extending into the anterior mediastinum and obliterating the clear retrosternal space may be seen. A scalloping of the posterior surface of the sternum could suggest internal mammary lymph node involvement (Fig. 6A). Also, it is important to determine if bony destruction of the manubrium, sternum or xiphoid is present (Fig. 6B). The latter is difficult to assess in routine anteroposterior and lateral views of the chest and even oblique sternal views; tomograms are essential. Three cases of sternal destruction were found by the tomographic technique (Fig. 7, A and B). The value of this study has been mentioned by other authors.9 The defects are usually marginal-lytic with some blastic reaction—and can be more extensive than the surface presentation of the lesion.

Associated hilar, pleural and parenchymal



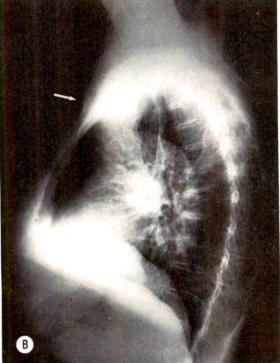


Fig. 6. Diagnostic roentgenographic appearances. (A) Mass in the retrosternal area is seen on lateral roentgenogram. (B) Destruction of the manubrium is associated with a mass in the superior mediastinum.

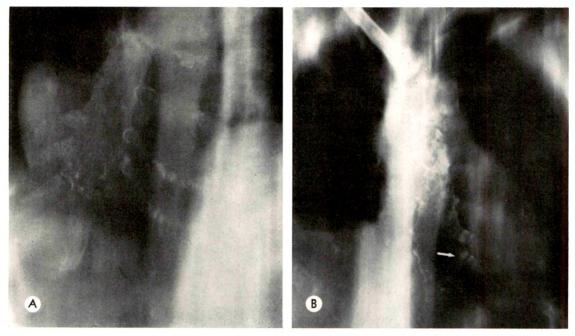


Fig. 7. Diagnostic tomographic appearances. (A) Normal sternal tomogram. (B) Destruction of the lower part of the body of the sternum.

changes are less specific signs. They could result in retrograde spread into the internal mammary nodes or could be part of a more generalized process.

## ASSOCIATION OF MEDIASTINAL DISEASE WITH I.M.L.N.M.

The high association of mediastinal disease and I.M.L.N.M. is an important feature to both the detection and management of I.M.L.N.M. recurrences (Table III). Nine instances of mediastinal involvement were found, but in 6 cases the full degree of spread was determined only after additional studies were made, and on 2 occasions mediastinal disease preceded the discovery of I.M.L.N.M. Superior vena cava obstruction was also present on 2 occasions (Fig. 8). One patient had recurrent pleural effusions, which were unexplained for months and transudate in nature, until a bluish nodule appeared at the sternal xiphoid junction. This occurrence indicates mediastinal compression secondary to internal mammary lymph node disease (Fig. 9). From the point of view of management, it is essential

not to treat the superficial nodule, which appears as a simple skin recurrence. An awareness of the pathways of extension is essential to determine the geometry of the field arrangement. Since most patients have not been treated with irradiation, problems of overlapping fields are not a factor. Once mediastinal disease is found to be present, larger fields are required and the depth dose will shift to a deeper level. In fact, our current philosophy is to treat all I.M.L.N.M. as if the whole mediastinum were involved.

## TREATMENT, SURVIVAL AND PROGNOSIS OF I.M.L.N.M.

The field arrangements and depth dose level changed as our experience increased. For the uncomplicated metachronous I.M.L.N.M., presenting as the first and only metastasis, chances for long-term control may be possible. A vigorous course of irradiation is recommended: the entire ipsilateral internal mammary lymph node chain and mediastinum are treated *en bloc*. The minimal depth dose to the mediasti-

TABLE III
ASSOCIATED RECURRENT DISEASE

	No.	Per Cent
I.M.L.N.M. as First Recurrence	6/16	37
Superior Vena Cava Obstruction	2/16	12
Mediastinal, Lung or Pleural Disease	9/16	56
Skin	2/16	12
Contralateral Axilla	5/16	32
Supraclavicular	1/16	12
Multiple Distal Metastases	2/16	12

num at 10 to 12 cm. level, midline, is 4,000 rads; the maximal dose of 5,000 rads at 3 cm. anteriorly is given through opposed biased fields. An additional booster dose of 500 to 1,000 rads may be given to the involved I.M.L.N.M. site. Depending on tolerance and field size, the daily depth dose is 150 to 200 rads. The area over the internal mammary nodule or mass should be bolused since skin invasion is so frequent, and, if the field size is not excessively wide, the contralateral internal mammary lymph nodes should be included.



Fig. 8. Superior vena caval obstruction associated with internal mammary lymph node metastases is demonstrated.

The more complex patients include those with disseminated or multiple metastases appearing simultaneously with I.M.L.N.M., contralateral I.M.L.N.M., and those with 2 primary lesions. Extensive mediastinal, pleural or pulmonary parenchymal findings demand optimum treatment planning. Each patient needs separate consideration, and no more than general guidelines can be offered. In 2 instances where small fields which did not include the whole internal mammary chain were used, a second ipsilateral I.M.L.N.M. appeared II and 3 years later respectively.

## THE ARGUMENT FOR ELECTIVE TREATMENT OF THE INTERNAL MAMMARY CHAIN

The keen observation of Sampson Handley (1927)<sup>11</sup> indicated that more than half of

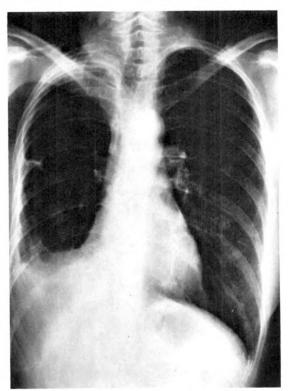


Fig. 9. Pleural effusion is associated with mediastinal involvement and internal mammary lymph node metastases. Pleural fluid and pleural biopsy were repeatedly negative, and diagnosis was not made until internal mammary lymph node metastases appeared.

recurrences found in operable breast cancer patients consisted of lymph node enlargement at the sternal border in the lower inner angle of the first 3 intercostal spaces. Two decades later, his son, Richard Handley (1947)9 and A. C. Thackray established the frequency of involvement of the internal mammary lymph nodes and related the incidence or risk to the presentation of the primary lesion and the axillary lymph node disease. In 250 cases of breast cancer, of which 61 were inner quadrant primary lesions, the incidence of positive internal mammary lymph nodes ranged to approximately half of the patients. Numerous other investigators doing routine biopsies at the time of radical mastectomy have confirmed that the percentage of microscopically involved internal mammary lymph nodes ranges from 10 per cent to 30 per cent, depending on the location of the primary breast cancer.

Important to oncologists is Sampson Handley's12 suggestion that internal mammary lymph node recurrences could be reduced by implanting radium tubes along the course of the internal mammary artery above the first rib and at the inner ends of the intercostal spaces. The need to focus on the internal mammary lymph node chain, as well as on the axillary lymph nodes, is the essence of present-day controversy among surgeons and radiation therapists concerning the best method of treating operable breast cancer in Stages 1 and II. The major limitation of the classic radical mastectomy procedure is its failure to cope with the internal mammary lymph node chain. Although the contention by Haagensen and Obeid8 was that such involvement obviated the use of radical mastectomy, others have chosen to use en bloc resection<sup>22</sup> or postoperative irradiation of internal mammary lymph nodes.7

It is inconsistent to argue for a prophylactic or elective axillary lymph node dissection, the cornerstone of radical mastectomy in Stage I breast cancer patients, while arguing against active intervention for the internal mammary lymph nodes,

particularly those with medial quadrant lesions of a similar stage. Evidence of the ability of irradiation to eradicate microscopic deposits in internal mammary lymph nodes is indisputable. In 1953, Rigby-Jones<sup>15</sup> reported no evidence of parasternal recurrence when postoperative radiation therapy included the internal mammary lymph node chain as compared to a 5.3 per cent incidence when it was not irradiated. In a later study, Smithers and Rigby-Jones (1959)<sup>17</sup> found 65 parasternal recurrences (observed as the first sign of recurrence) following radical mastectomy; in most instances the internal mammary lymph node chain was not irradiated. Only 4 of the 65 had clinical evidence of parasternal lymph node involvement after receiving parasternal irradiation. Also, the findings of the M. D. Anderson Hospital series<sup>23</sup> in which 4 parasternal nodules appeared in 282 patients, with tumors located centrally or medially, demonstrate the effectiveness of elective irradiation of the homolateral internal mammary lymph nodes. As mentioned previously, the zero incidence of a parasternal recurrence in more than 300 patients routinely irradiated with inverted L arrangements in our division further corroborates the effectiveness of irradiation in controlling this problem locally.

Urban<sup>21,22</sup> represents the single major exponent for surgical en bloc resection of the internal mammary lymph node chain in operable breast cancer. The basis for his support of this extended procedure rests on the lower survival rates for similarstage breast cancer patients with inner quadrant vs. outer quadrant lesions. In 1958, Treves and Holleb,20 reporting on the salvage of women 35 years of age or younger with breast cancer, demonstrated an 8 per cent lower incidence of 5 year survival for Stage I inner quadrant vs. outer quadrant primary lesions with negative axillary lymph nodes. If the axillary lymph nodes were positive, the difference in survival was much greater: 47 per cent vs. 69 per cent respectively. Analyses of 1,000 consecutive cases

of primary breast cancer patients at Memorial Hospital in New York showed an 11 per cent difference in 5 year survival favoring lateral quadrant lesions, i.e., 71 per cent vs. 82 per cent. This difference was attributed to the high incidence of internal mammary lymph node disease with central and inner quadrant lesions and positive axillary lymph nodes. It has been substantiated by analyses of Urban's21 dissected internal mammary lymph nodes: a 20 per cent incidence presented as 13 per cent if the axilla was negative, but if the axilla was positive, ranged as high as 40 per cent. Thus the value of extended resection rests in the low 2 per cent recurrence rate. But the use of postoperative irradiation in half of the cases with positive lymph nodes (internal mammary and axillary lymph nodes) obscures the benefits that can be attributed to en bloc resection of the internal mammary lymph nodes alone.22 This entire argument has been challenged by the recent national study in which no difference in survival was found after radical mastectomy based upon location of the primary lesion in the breast.22

I.M.L.N.M. appearing as the first and only recurrence after radical mastectomy is managed by aggressive radiation therapy. The treatment of the parasternal nodule as an isolated finding is conceptually unrealistic. Since long-term control is possible, and has been reported, a larger field is advocated to include the entire homolateral internal mammary lymph node system. In reality, the incidence of I.M.L.N.M. disease is even higher if one includes all recurrences appearing as mediastinal disease in this category, as well as parasternal nodules. The incorporation of the first 3 interspaces to prevent contralateral spread may be used, but the low incidence of such a development argues against extension of the field routinely. Of the 65 patients reported by Smithers and Rigby-Jones, 17 14 were alive and well at the time of the report, and 42 per cent of the cases survived more than 2 years after treatment of these recurrences. Additional long-term survivors were noted by Sanger<sup>16</sup> in 2 of 8 living cases, 5 and 7 years post radiation therapy, respectively.

The most critical and thorough review of selective vs. elective irradiation of internal mammary lymph nodes is that of Haagensen et al.7 based upon their triple biopsy procedure. The results of management by irradiation of localized breast cancer patients found to have positive internal mammary lymph nodes in biopsy have dropped, according to Guttmann's reports, from 50 per cent at 5 years to 11.3 per cent at 10 vears. Haagensen's new treatment plan is radical mastectomy for all localized breast cancers (Columbia Stage A and B), followed by irradiation of the internal mammary lymph nodes electively, except for those outer quadrant lesions less than 3.0 cm. in diameter. The experience reported in his clinic and literature indicates a 20 per cent occult incidence of I.M.L.N.M. His data illustrate that positive parasternal lymph nodes are incised by this procedure, which may also disseminate the disease. Also, the triple biopsy procedure has been used by Handley and Thackray, who have had the best 10 year survival figure, i.e., 20 per cent in 80 patients with positive internal mammary lymph nodes. The important facet of Haagensen's procedure is the abandonment of selective irradiation of internal mammary lymph nodes for elective irradiation.7

## CONCLUSION

The most important statement to emerge in the recent literature on breast cancer is that elective irradiation of internal mammary lymph nodes can eradicate the development of internal mammary lymph node metastases. The ability of irradiation to control microscopic deposits in internal mammary lymph nodes, as well as axillary lymph nodes, has been established. The ability of surgery to do the same has also been proven by the low axillary recurrence rates after axillary dissection of  $N_{\rm 0}$  lymph nodes which proved to be  $N_{\rm +}$  on micro-

scopic examination. The effect on later survival is not known since a precise, comparative classification of breast cancer is not generally used: criteria for staging on clinical or surgical grounds are often unclear, the specific percentage of irradiated patients is seldom detailed in surgical reports, and also, the reason for failure or exact pattern of recurrence is not detailed. If patients with a positive internal mammary lymph node biopsy (similar to patients with positive subclavicular or axillary apex lymph nodes) have recurrences initially at distant metastatic sites, without evidence of local or lymph node recurrence, no modification or combination of local therapies will alter the course of the disease. The evidence from Haagensen et al.7 is that patients with occult axillary and/or internal mammary lymph node metastases are salvageable and deserve treatment.

The important therapeutic issue that remains undefined from this line of evidence is not whether to treat occult lymph node metastases in localized breast cancer, but whether irradiation should be consistently used in all potential sites, rather than a combination of both methods, as is currently the practice. By contrast, Crile<sup>3</sup> emphasizes the importance of uninvolved regional lymph nodes in maintaining systemic immunity and argues for retaining the lymph nodes, not offering routine axillary dissections.2 His experimental evidence illustrates clearly that the major advantage of elective irradiation vs. elective surgery is the reconstitution of lymph nodes after irradiation, thereby restoring immunity.3

Simple vs. radical mastectomy is another version of selective vs. elective lymph node treatment, but the focus is on the axillary lymph nodes. The need for accurate information and careful study requires that cooperative trials be established to resolve the vexing problem as to whether to treat No lymph nodes—and by which method or combination of methods—in order to yield the best local and distant control of the disease. Such a cooperative protocol is being

developed by the Surgical Adjuvant Group and should be actively supported.

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## ROENTGENOGRAPHIC FEATURES OF MULTICENTRIC CARCINOMA OF THE BREAST\*

By DAVID A. LEGGE, M.B., D.M.R.D., and DAVID M. WITTEN, M.D. ROCHESTER, MINNESOTA

MULTICENTRIC carcinoma of the breast can be described as a condition in which two or more primary independent foci of carcinoma exist concurrently within the ductal system of a breast. These foci may be widely separated by cancer-free tissue or may occur in relative continuity within a single ductal system. While not often recognized clinically, numerous anatomic studies have shown that carcinoma of the breast of multicentric origin is not infrequent. Qualheim and Gall<sup>4</sup> found more than one nidus of carcinoma in 54 per cent of 157 breasts surgically removed for carcinoma; in 17 per cent, the lesions were confined to a single quadrant, and in 37 per cent, different quadrants of the breast were involved by unconnected tumor. Anatomic studies by Tellem, Prive, and Meranze<sup>7</sup> and by Gallager and Martin<sup>2</sup> have vielded a similar incidence of multicentricity in carcinoma of the breast.

The clinical significance of multicentricity in carcinoma of the breast is unknown, but some authorities think that the demonstration of multicentricity may have therapeutic as well as prognostic implications. For example, Robbins and Berg<sup>5</sup> in a follow-up study of 1,658 patients treated for mammary carcinoma found a higher incidence of second primaries in the remaining breasts of those patients who were found to have multicentric carcinoma in the previously removed breasts. Leis and associates3 recommend prophylactic mastectomy of the second breast of a patient with multiple primaries, on the premise that such a patient is at higher risk for developing a new primary in the remaining breast than is a patient with unifocal carcinoma.

Mammography has an established role in the detection and localization of carci-

noma of the breast.<sup>1,6</sup> This role logically also should include, if possible, the detection of multiple sites of origin of tumor. It

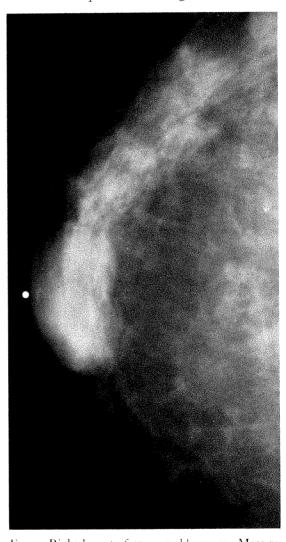


Fig. 1. Right breast of 50 year old woman. Mass remained unchanged in size for 2 years. Right simple mastectomy was performed. Pathologically, lesion was multicentric Grade 1 mixed papillary and comedo adenocarcinoma. Mammogram shows multiple well-defined nodules in right breast, resembling benign disease.

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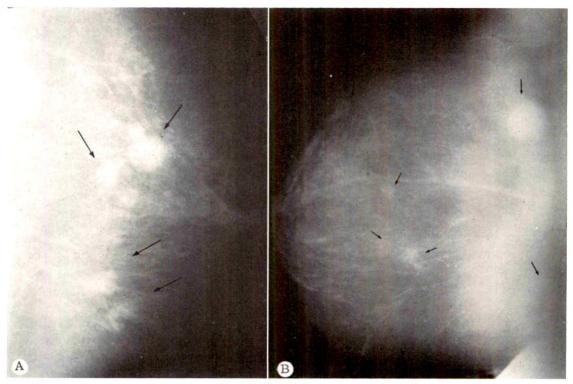


Fig. 2. (A) Left breast of 57 year old woman who recently had discovered a 3 cm. firm mass therein. Left radical mastectomy was performed. Pathologically, lesion was multicentric Grade 3 scirrhous adenocarcinoma; multiple nodules measured up to 1.5 cm. in diameter and were scattered throughout breast. Mammogram shows several irregular nodules (arrows) with various amounts of normal breast tissue interspersed. (B) Right breast of 58 year old woman who recently had discovered a lump therein. Right simple mastectomy was performed. Pathologically, there were 5 areas of scirrhous adenocarcinoma scattered throughout breast tissue. Mammogram shows multiple irregular nodules.

is the purpose of this paper to describe some roentgenologic features of multicentric carcinoma of the breast, which may be of assistance in the preoperative identification of this condition.

## MATERIAL AND METHOD

The histories of all patients coded as having multicentric carcinoma of the breast during a 3 year period at the Mayo Clinic were reviewed. The diagnosis was established by the usual random sectioning of breasts removed at operation for carcinoma. Forty-seven cases with preoperative mammograms were available for study.

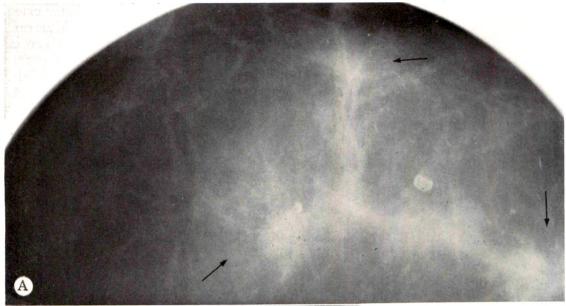
## RESULTS

The diagnosis of multicentric carcinoma of the breast could be suggested from the

roentgenographic changes in 26 of the 47 mammograms available. In 14, a single mass of carcinoma could not be identified as multicentric, and in 7, there was no evidence of carcinoma.

In 4 of these last 7 cases the involved breasts were too small and dense for detection of the lesions, and in 2 the nodules were too small to be seen on the film. In the remaining case, there were multiple nodules, but these were well defined and the appearance of the breast mimicked that of benign disease (Fig. 1).

In 8 of the 14 cases in which the diagnosis of malignant disease was established but multicentricity could not be suggested, the mass was too diffuse for detection of the individual nodules. In 4, the second nodule was small and could not be separated from



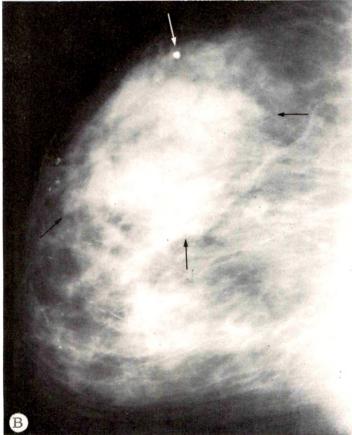


Fig. 3. (A) Right breast of 72 year old woman who had discovered induration beneath nipple 6 months previously. Right radical mastectomy was performed. Pathologically, lesion was diffusely infiltrating Grade 4 scirrhous adenocarcinoma with multiple nodules. Mammogram shows large area of cancerous tissue in which nodules can be seen (arrows). (B) Mass in left breast of 89 year old woman. Lesion was discovered during routine physical examination. Left radical mastectomy was performed. Pathologically, tumor was diffuse, multicentric Grade 3 mixed comedo and infiltrating adenocarcinoma. Mammogram shows large mass in which individual nodules can be seen (arrows).

dense breast tissue; and, in 2, the breasts were too small and dense to permit evaluation of a second lesion.

Analysis of the mammograms of the 26 cases in which the diagnosis of multicentricity could be suggested revealed two

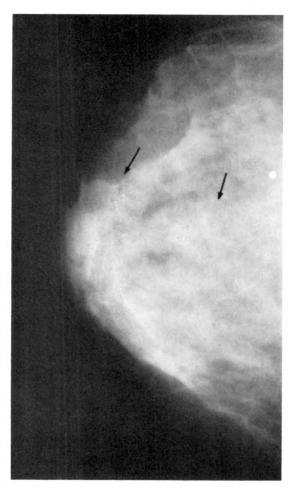


Fig. 4. Right breast of 36 year old woman who discovered nodule therein 3 months previously. Right radical mastectomy was performed. Pathologically, lesion was multicentric Grade 3 scirrhous adenocarcinoma. Mammogram shows 2 areas containing stippled calcification (arrows) separated by normal breast tissue.

basic patterns. In 15 of the cases, two or more nodules could be seen. Each of these nodules individually presented the usual characteristics of malignant disease; *i.e.*, the mass was discrete, had a dense center, and had irregular indistinct margins infiltrating the surrounding breast parenchyma. These masses varied in size and location. In some, there were large areas of cancerfree tissue interspersed between the nodules (Fig. 2, A and B). In others, there was a large area of carcinomatous involvement in which separate identifiable nodules could be seen, but the intervening parenchyma

was involved to a greater or lesser extent by carcinoma (Fig. 3, A and B). Most cases could be classified between these two extremes, with various amounts of cancerfree tissue interspersed between the nodules.

In 9 of the cases, the malignant disease of the breast was apparent from the presence of the numerous irregular punctate calcifications characteristic of malignant



Fig. 5. Left breast of 70 year old woman. Nodule was discovered on routine physical examination. Left radical mastectomy was performed. Pathologically, lesion was diffuse multicentric Grade 3 mixed papillary comedo and scirrhous adenocarcinoma. Mammogram shows stippled calcification associated with small irregular nodules extending along ducts beneath nipple (arrows).

tumor. Multicentricity could be suggested in all of these cases. In 4, the calcifications were in separate locations, with intervening cancer-free breast tissue (Fig. 4). In 2, the calcifications were associated with multiple small nodular densities which were irregular in outline and extended along ducts to nipple (Fig. 5). In the other 3 cases, the calcifications were of unusually wide distribution, ramifying throughout

the ductal system of an entire lobule (Fig. 6, A and B).

In 2 of the 26 cases, a combination of these two patterns was noted, a malignant nodule in one area being separated by cancer-free breast tissue from an area containing characteristic calcification (Fig. 7).

## COMMENT

The preoperative roentgenographic iden-

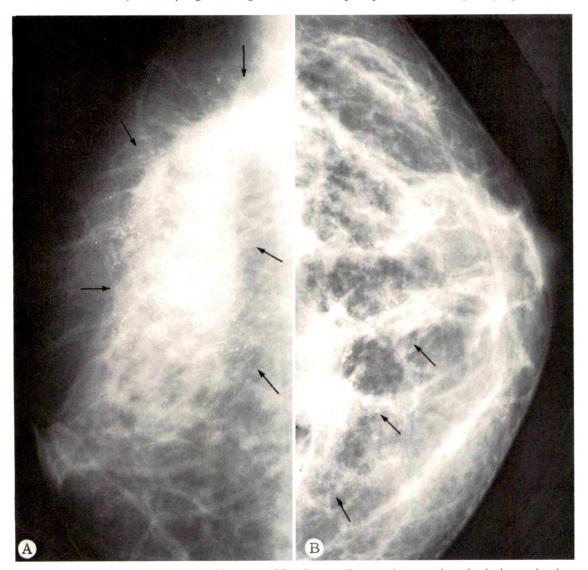


Fig. 6. (A) Right breast of 68 year old woman. Nodule was discovered on routine physical examination. Right radical mastectomy was performed. Lesion was multicentric Grade 3 comedo and infiltrating adenocarcinoma. Mammogram shows unusually large area of stippled calcification (arrows). (B) Left breast of 46 year old woman who recently discovered nodule therein. Left radical mastectomy was performed. Pathologically, lesion was multicentric lobular comedo and scirrhous Grade 4 adenocarcinoma. Mammogram shows prominent stippled calcification extending throughout ductal system of lobules (arrows).

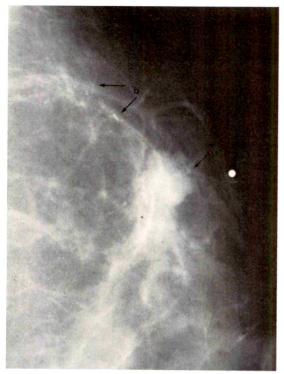


Fig. 7. Right breast of 63 year old woman who recently noted nodule therein. Right radical mastectomy was performed. Pathologically, lesion was multicentric Grade 2 comedo adenocarcinoma. Mammogram shows irregular nodule (a) separated by normal breast tissue from area of stippled calcification (b).

tification of multicentric carcinoma is occasionally difficult or impossible, because a large mass of carcinomatous tissue may obscure independent foci of carcinoma or lesions may not be identifiable on the roentgenograms. However, the multicentric character of carcinoma of the breast frequently can be suggested, and this may be of assistance in the preoperative and postoperative management of the patient. The multicentric character of carcinoma of the breast in this series was evident in more than half the mammograms. The diagnosis can be suggested with good reliability on mammograms in which 2 or more malignant nodules are demonstrated or in which intraductal calcifications are extensive. linear in distribution, or separated by normal breast parenchyma from other areas of obvious carcinomatous involvement.

Because of possible therapeutic and prognostic implications, it seems prudent that the radiologist suggest the diagnosis of multicentric carcinoma when these features are observed.

## SUMMARY

Roentgenographic evidence of multicentricity was present in 26 of 47 cases of multicentric breast carcinoma in which the preoperative mammograms were reviewed.

Some of the features observed in these cases were the presence of 2 or more nodules, separation of areas of calcification or other unusual distribution of calcific deposits, and the presence of both a nodule and a separate area of calcification.

Because of possible therapeutic and prognostic implications, it seems prudent that the radiologist suggest the diagnosis of multicentric breast carcinoma when these features are observed.

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## UNIQUE CHEST ROENTGENOGRAM IN SCLERODERMA\*

By JACK ZUCKNER, M.D.,† and JAMES MARTIN, M.D.‡ st. louis, missouri

THE protean manifestations of scleroderma are well recognized, consisting primarily, of alterations in the skin, lungs, heart kidneys and gastrointestinal tract. In the course of evaluating a patient with this connective tissue disease, an unusual finding was discovered on chest roentgenography. This unique observation is reported.

## REPORT OF A CASE

E.N., a 41 year old white female, was admitted to St. John's Mercy Hospital for the eighth time with a diagnosis of scleroderma. She first noted thickening of the skin at the age of 29 years. In the ensuing years the skin became thickened over widespread areas of the upper and lower extremities, thorax and abdomen. The face was spared. Of particular interest was the marked thickening of skin and subcutaneous tissues around the base and margins of both breasts, giving a cupcake-like appearance to the breasts (Fig. 1). Changes in the upper extremities were also unusual in that skip areas of involvement gave the impression of normal skin escaping from underneath thickly tightened skin.

The lungs and possibly the heart were thought to have sclerodermatous changes. Basilar rales were heard in both lungs on numerous occasions. Pulmonary function tests revealed evidence of restrictive lung disease. Vital capacity was 58 per cent of normal. Forced expiratory volume was 56 per cent of normal at 0.5 second and 51 per cent of predicted normal at 1.0 second. At 3 seconds it was 78 per cent of normal. Forced vital capacity was 61 per cent of normal. The heart was negative on examination. Electrocardiograms revealed nonspecific ST and T wave changes.

The patient had repeated episodes of thrombophlebitis in both calves. On one occasion she developed cellulitis in a leg. Ulcerations had

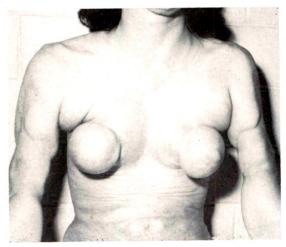


Fig. 1. Sclerodermatous involvement about both breasts.

occurred several times on the lower portion of both legs in the early years of her illness. One plus albuminuria was found during an episode when the patient had a high fever, but this was not considered suggestive evidence of sclerodermatous renal involvement since the albuminuria disappeared when the temperature returned to normal. The blood urea nitrogen was normal on several testings. There was no symptomatic or roentgenographic evidence of gastrointestinal tract pathology. On a recent admission to the hospital the patient had marked dizziness which was thought to be due to labyrinthitis, the etiology of which was undetermined. There was no history of Raynaud's phenomena. The patient was allergic to penicillin.

The complete blood cell count was normal on most testings. Serum electrolytes were normal. Urinary levels of 17 hydroxycorticosteroids and 17 ketosteroids obtained while the patient was on steroid therapy were decreased. ACTH stimulation over a 10 day period did not result in significantly increased urinary

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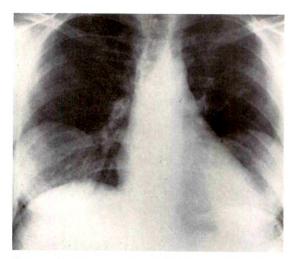


Fig. 2. Roentgenogram of the chest reveals large circular opacities in the breast regions due to scleroderma of the soft tissues about the breasts.

steroid values. A sedimentation rate was 34 mm./hour. The latex test for rheumatoid factor was negative.

The patient was treated with steroids and para-aminobenzoic acid (PABA) during most of her illness. Her steroid dose for the past few years had been 2 mg. triamcinolone daily for the most part, but at times she received 6 mg. daily in divided doses. The PABA dose was 2 gm. 4 times daily. This therapy had resulted in slightly less stiffness and swelling.

Chest roentgenograms revealed slightly accentuated markings at the base of each lung, but there was no specific evidence of infiltration, consolidation or pleural effusion. Of marked interest was a large grapefruit-sized opacity noted in the area of the breast on each side of the chest when examined in the posteroanterior projection (Fig. 2). The lateral pro-

jection indicated that the opacities were not pulmonary in origin, but were related to overlying breast and subcutaneous tissue pathology. The cardiac shadow appeared normal.

## DISCUSSION

The unusual appearance on chest roentgenograms of large opacities in the breast regions in a patient with scleroderma would not likely be confused with pulmonary pathology. Localization of the source of this abnormality to tissues outside the lungs could be readily discerned by a lateral chest roentgenogram. Large pulmonary masses might, however, simulate this appearance in the posteroanterior roentgenogram in rare cases. Also to be differentiated would be breast shadows caused by injections into the breasts of silicone or other foreign material for cosmetic purposes.

In the case described, the thickening, scarring, and folding of the sclerodermatous tissues about the breasts were apparently responsible for the unique roentgenogram.

## SUMMARY

A rare chest roentgen finding is described of scleroderma causing large opacities in both breast regions due to involvement of the soft tissues in these areas.

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## PRACTICAL ASPECTS OF BETATRON ELECTRON BEAM DOSIMETRY\*

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WHEN our institution acquired a betatron unit our particular interest was in exploring the possible benefits to be derived from the unique dose distribution which the electron beam would permit. Although we had some previous experience with electron beam therapy, the difficult and complex problems involved in dosimetry were not fully developed.

This presentation is concerned with some of the practical methods we have evolved for dealing with these problems.

## METHOD

The routine monitoring of electron beam exposure rates and total exposure is conventionally done with parallel plate ionization chambers. Since machine on-time is governed by these important devices, it is first necessary to consider their role in the dosimetry picture.

The limited precision of these rugged instruments requires periodic absolute intercalibration by other methods, such as thimble ionization chambers, chemical dosimetry, or calorimetry. On newer machines similar to ours the manufacturer has replaced the original monitoring system control with a solid-state control mechanism. but we are pleased with the performance of the original system and have modified it to facilitate the daily calibration routine used at our institution. Figure 1 is a block diagram of the monitoring system. The essential changes consist of incorporation of external ten-turn potentiometers for fine adjustment of dose rate, dose zero, and "R"/min. meter zero controls. An internal light and "viewing window" permit observation of the tachometer generator speed, which is directly proportional to the ionization current produced in the parallel-plate monitor.

The daily calibration procedure consists of adjusting the exposure counter speed to attain 10 "R"/click in the x-ray beam calibration, as measured by Victoreen thimble chamber in the equilibrium block; "R"/click refers to beam monitor counts or "clicks." Thus, if the output were found to be 9.0 "R"/click, we would reduce the electrical signal to the tachometer generator by dose rate potentiometer change, so that the counter revolutions per unit time would be less, requiring more beam time to get the desired 10 "R"/click.

Because only 25 meV. x rays are used from the dual-beam donut, and electron beam energies are varied from 10–25 meV., it is convenient to key electron beam calibrations to the arbitrary 10"R"/click setting for x rays. That is, once the monitor is set for the x-ray calibration, we measure the actual "R"/click for the different electron beam energies to be used each day. The stability of this arrangement has been verified by remeasuring the x-ray calibration after a treatment schedule of several hours, and the 10 "R"/click reproduces to within 2 per cent. This system has been used successfully for several years.

## DISCUSSION

The question of the precision of the betatron manufacturers' statement of electron beam energy has existed for some time. The console dial setting values are actually calculated by the manufacturer, rather than measured experimentally. The reason for this is obvious: energy measure-

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<sup>\*</sup> Presented at the Seventy-first Annual Meeting of the American Roentgen Ray Society, Miami Beach, Florida, September 29-October 2, 1970.

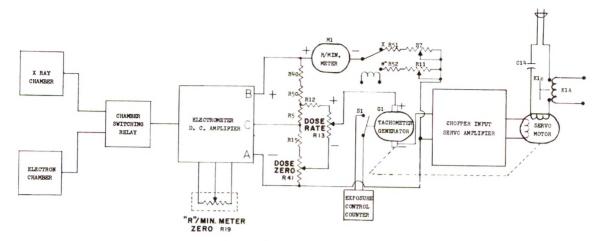


Fig. 1. Betatron beam monitor block diagram.

ments are not simple to obtain. A workable method of measuring beam energy involves range vs. energy measurements in water phantoms. An empirical range-energy equation is used with the measured data to estimate the actual beam energy<sup>3</sup>. We have made several determinations by the latter method and have found the dial settings to be within 10 per cent of the measured values.

Some opinion has come forth challenging the validity and need for energy measurements. Since the beams are used to treat at tissue depths, it is felt that more meaningful information would be derived from good depth-dose data for the particular dial settings.

Film dosimetry has been used as our principal means of obtaining electron beam dose distribution data.¹ Although film dosimetry can present considerable sources of error, we feel that our technique is now sufficiently precise to provide reproducible information with relatively little difficulty.

Meaningful dose data from film require use of proper film in reasonably well simulated phantoms. Unit-density depolymerized rubber is used to sandwich readypack industrial film (Type M) in the securely clamped phantom. This arrangement assures minimal occlusion of air, which would result in differential fast electron scatter with consequent greater film darkening. Film characteristic curves have been obtained with Type M industrial film for several electron beam energies and show excellent linearity in the exposure region of interest.<sup>1</sup>

Densitometry of properly exposed and processed film can also be subject to various errors. We have employed a semi-automatic densitometry set-up described elsewhere.1 The exposed film is positioned in the output-writer carriage and caused to move past a fixed photocell in a predetermined pattern analogous to paper in a typewriter carriage. The electrical signal from the photomultiplier tube is fed to the densitometer and the PPDVM (printing per cent digital voltmeter) provides visual display of relative density readings and output-writer print-out. This print-out shows 5 per cent gradations of maximum film density. Figure 2 reveals the densitom-

Fig. 3. Composite picture of data from absorbed dose measurements and film dosimetry for 24 meV. electron 10×12 cm. field. Numbers in small rectangle represent FeSO<sub>4</sub> values, showing correlation with film dosimetry.

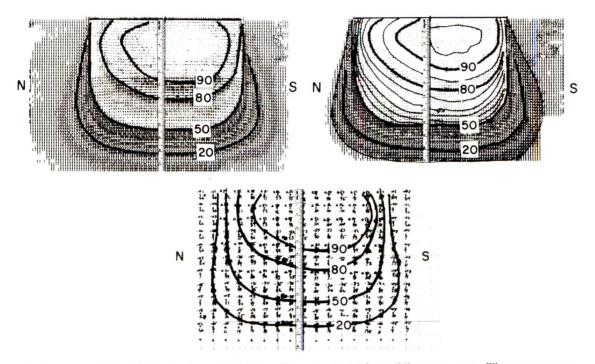
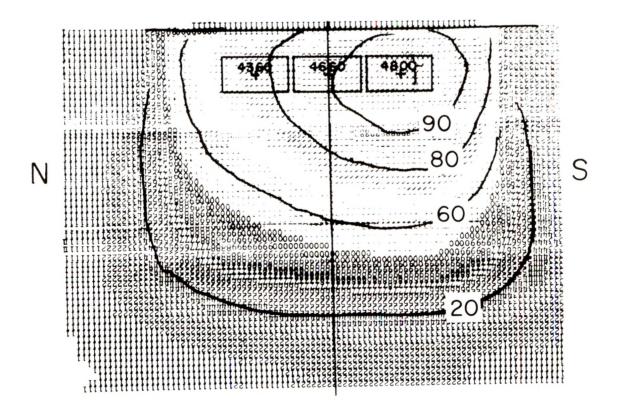


Fig. 2. Electron beam dosimetry (24 meV.). Same film quantitated by 3 different systems. The upper 2 were measured on different semi-automatic densitometers, while the lower isodose curves were obtained from a manual densitometer.



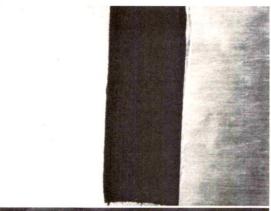




Fig. 4. Superficial lesion being treated by modified 10 meV. electron field.

etry of a film exposed to 24 mev. electrons. This film was densitometered on our Artronix densitometry set-up and on our Welch densitometer by hand. It was then densitometered on another Artronix set-up at St. Francis Hospital in Indianapolis. The excellent similarity of the print-outs can be seen; e.g., the depth of the 50 per cent isodose is very close for all 3 print-outs.

The foregoing development offers a convincing argument for the use of film in relative dose applications. We have intercompared electron beam film dosimetry with data obtained from ionization chambers and from FeSO<sub>4</sub> chemical dosimetry.

The agreement was found to be remarkably good. Figure 3 shows a composite picture of data derived from all 3 dosimetry techniques. The particular dose distribution shown is in the so-called north-south plane (parallel to the donut) of a 24 mev. electron 10×12 cm. field. Asymmetry in this plane is quite pronounced, as is clearly seen from the film print-out. Superimposed on the print-out are the approximate size and location of the FeSO<sub>4</sub> cells that were placed in this field subsequently, as a part of the National Bureau of Standards electron beam uniformity study. The outer pair were irradiated simultaneously and the center cell was exposed separately. In order to estimate the absorbed dose in rads to the FeSO<sub>4</sub> cells, thimble ionization chamber data are taken in the same locations in the SCRAD<sup>3</sup> phantom (equilibrium depth 1.5 cm. from the surface of a polystyrene slab). The ionization chamber readings are multiplied by C<sub>F</sub> factors<sup>2</sup> to convert "R" to rads. The estimated rads are then compared to the rad values determined by FeSO<sub>4</sub> dosimetry at the National Bureau of Standards. Our rad values differ from those measured at the National Bureau of Standards by less than  $\pm 5$  per cent.

The important point to be seen in Figure 3 is that film dosimetry establishes very well the field asymmetry, as confirmed by chemical and ionization chamber dosimetry. In fact, neither of the latter methods can yield as fine resolution of dose distribution as our film technique because of the larger physical size of FeSO<sub>4</sub> cells or thimble chambers. Also, positioning of these detectors in the field may vary, whereas exposure to a properly loaded film phantom does not present this problem.

A clinical example to demonstrate the efficacy of film dosimetry is shown in the following illustrations. Figure 4 shows a patient with a large, neglected basal cell carcinoma being treated with a modified 10 meV. electron field. This lesion measured 8×7 cm. Its size precluded conventional therapy with superficial roentgen irradiation and since we have a negligible

output, below 10 meV., a 1.5 cm. paraffin bolus was used to raise the skin dose to 100 per cent and to avoid treatment below a depth of 3 cm. Figures 5 and 6 demonstrate the effectiveness of the 1.5 cm. bolus in achieving this goal. The 50 per cent isodose line is now about 1.7 cm. deep from the surface instead of 3.3 cm. The horizontal phantom view shows the efficient shielding of \(\frac{1}{8}\) inch lead for peripheral shielding. Figure 7 shows the lesion near the end of treatment. The observed effect on both tumor and normal skin is commensurate with what one would observe from a course of superficial roentgen therapy under a similar fractionation schedule.

The effect of tissue inhomogeneity must also be considered in electron beam dosim-

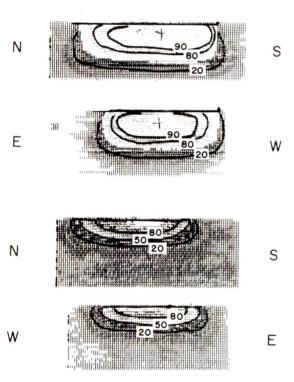


Fig. 5. Comparison of depth dose distribution for unmodified and modified 10 meV. electron field used for treatment shown in Figure 4. Factors: 10×12 cm. field size at 100 cm. source skin distance; 0.010 inch Pb+0.027 inch Al scatterer. Upper: Parallel to donut. Upper mid-central: Vertical to donut. Lower and lower mid-central: Same factors+1/8 inch Pb peripheral shielding and 1.5 cm. bolus intraorally.

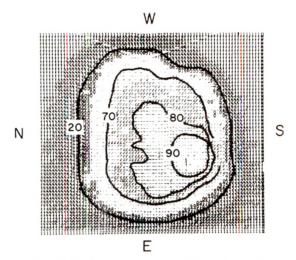


Fig. 6. Horizontal phantom plane view of the modified 10 meV. electron field.

etry. At the present time, we compensate for this by considering the electron densities of the various tissues in the beam; e.g., the ratio of the electron density of wet

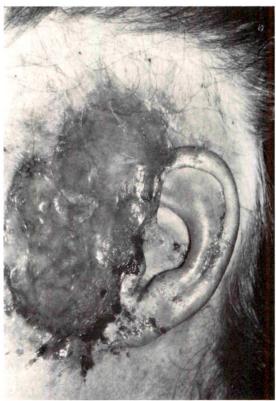


Fig. 7. Appearance of lesion in final stages of treatment by the modified 10 meV. electron field.

soft tissue to bone is in the range of 1.65, or 1 cm. of bone is equivalent to 1.65 cm. of wet soft tissue. Phantom studies are in progress to quantitate more accurately the effect of tissue inhomogeneities on dose distribution.

## SUMMARY

Some of the problems of electron beam calibration and dosimetry are presented along with practical methods of handling them. Without such methods, accurate dosimetry would be most difficult to obtain.

Film dosimetry has been especially useful in giving us a reproducible method of rapidly determining accurate dose distributions.

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# A RANDOMIZED STUDY OF HYPERBARIC OXYGEN AS AN ADJUNCT TO REGULARLY FRACTIONATED RADIATION THERAPY FOR CLINICAL TREAT-MENT OF ADVANCED NEOPLASTIC DISEASE\*

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THERAPEUTIC radiologists and radiobiologists have through the past 20 years pursued the concept of sensitizers of ionizing radiations in their effect on neoplastic tissue, with diligence and foresight. Gray and associates<sup>10</sup> in 1953 described the effect of oxygen on the radiosensitivity of living cells when subjected to radiation. Alper and Howard-Flanders1 noted that very small increases in oxygen tension in severely hypoxic tissue resulted in two- to threefold increases in radiosensitivity of mammalian cells subjected to irradiation. Thomlinson and Gray<sup>15</sup> in describing the histologic configuration of a squamous cell carcinoma of the bronchus as "cords of tumor cells surrounded by blood vessels" presented histologic evidence for the increased radiosensitivity of well-vascularized tumor tissue as compared with the sparse vascularity in large tumors. Clinical therapeutic radiologists, long aware of the increased radiosensitivity of the small wellvascularized neoplasms moved swiftly to apply these concepts to their patients with large, advanced neoplasms.

Churchill-Davidson and associates<sup>4,5</sup> in London reported their efforts with oxygen under pressure given as an adjunct to radiotherapy to patients with advanced neoplasms.

van den Brenk and his group reported their efforts with hyperbaric oxygen in 1961–62.<sup>12,16</sup> Wildermuth,<sup>17</sup> Atkins *et al.*,<sup>2</sup> and Plenk<sup>13</sup> followed with their experiences

in the use of hyperbaric oxygen as an adjunct to radiation therapy.

Because of the increasing interest in the subject of hyperbaric oxygen, the majority of those vitally interested in this subject met in November of 1965 at the First San Francisco Cancer Symposium to review the history, radiobiology, physics, and clinical experience of, and with, this modality, and to assess its present status and its future potential. As the symposium progressed the necessity for a prospectively randomized study of oxygen under pressure as an adjunct to radiation therapy, compared with radiation therapy alone, emerged as a recurrent theme. 14

We envisioned such a study and set about designing a suitable protocol which might lead to more enlightening results.

### CONCEPTS

Mindful of the observation that advanced tumors were the repository of hypoxic cells and, as such, responded less favorably than smaller, more oxygenated tumors to radiation therapy, we included in this study cancers of the head and neck, Stages T3, T4, N1 to N3, Mo; cervical cancer, Stage IIIA and IIIB and IV; bladder tumors, Stage C and D; recurrent carcinoma of the rectum—Duke's C; squamous cell carcinoma of the mid-third of the esophagus; and glioblastomas of the brain. Staging of the patient's disease was the consensus of 3

<sup>\*</sup> Presented at the Seventy-first Annual Meeting of the American Roentgen Ray Society, Miami Beach, Florida, September 29-October 2, 1970.

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different examiners employing all the usual techniques, including indirect and direct examination and roentgenographic evidence, but excluding surgical staging. Both sexes were accepted. An age limit of 75 years was imposed because of the necessity of patient cooperation inside the chamber. Minor cardiac conditions were not considered a deterrent. Pulmonary function tests were obtained if any question of respiratory inadequacy presented and, if such were verified, the patient was not admitted to the study. Randomization between hyperbaric oxygen with radiation therapy and radiation therapy alone was accomplished by a drawing at random by a disinterested person of a card designating one or the other of the modalities. The patient thus drawn was assigned to a pair grouping which was as alike as possible in area of disease and extent of disease. The patient thus randomly assigned to receive hyperbaric oxygen was given just enough information to

render an informed consent. A Picker C 10,000 unit was employed as the radiation source and this machine contraindicated the utilization of the Vickers chamber employed in the studies previously mentioned (Fig. 1). An American product of cantilever design was chosen because of its adaptation to the Picker C-arm principle rotating machine (Fig. 2). All hyperbaric oxygen patients were subjected to 3 atmospheres absolute (2 atmospheres, 29.4 pounds per square inch gauge) for a "soaking" period of 30 minutes based upon the equilibrium times from the observations of Evans and Naylor<sup>7</sup> and Bergofsky et al.,<sup>3</sup> who measured the pO<sub>2</sub> in lymph while breathing O<sub>2</sub> at 30 pounds gauge, and recorded values in the order of 600 mm. Hg pressure. Since only 3 atmospheres absolute of pure oxygen was utilized, it was not necessary to anesthetize the patients prior to compression and, in fact, it was found necessary to sedate the patients only during the first 5

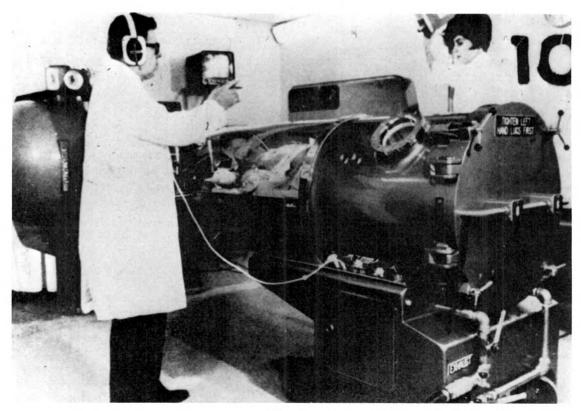


Fig. 1.



Fig. 2.

or 6 compressions. The total "soaking" time was confined to a period not longer than 30 minutes to conform with the observations of Churchill-Davidson<sup>6</sup> and Gillen<sup>9</sup> that oxygen under pressure is toxic to the central nervous system when exposure is prolonged, and that this toxicity is manifested earlier in the presence of carbon dioxide. If exposure to oxygen at 3 atmospheres absolute is confined to 30 minutes this toxicity is minimized, according to Frankenhauser et al.8 Since one-quarter of the chamber wall was constructed of a clear plastic substance, the patient was somewhat relieved of his feeling of confinement and was able to see and communicate with his doctor and the chamber technician. Closed circuit television cameras focused on the chamber and patient in both the oxygen preparation and cobalt unit rooms, and two-way radio communications added to this sense of security. Direct observations by the doctor of the patient's chest and facial muscular movements and carotid pulse proved excellent parameters of the patient's status. The patients removed all clothing, jewelry and hairpins. They were clothed in special fiberglass surgical gowns and dampened fiberglass surgical caps to minimize static electricity production. Fiberglass sheets provided comfort and warmth when they did not cover radiation fields. Increased chamber pressure caused some tympanic membrane sensitivity, usually in the younger rather than the older patients. Very few patients, however, required myringotomy and gum chewing served well to equalize the middle ear pressures during pressure changes.

The Picker C 10,000 unit with a 10,000 RHM source provided the radiation and, since transmission of the beam through the plastic decreased it only 5 per cent, no correction of the total dose was made. Important in our protocol deliberations at that time (1966) was the desire to utilize

the vast storehouse of knowledge and expertise gained with normal 5 day (1,000 rads per week) daily fractionation. Accordingly, it was decided to utilize our usual total dose peculiar to that anatomic area and histology, and fractionate daily in all cases admitted to study.

### TECHNIQUE

The patient admitted to the study and randomized to receive adjunctive hyperbaric oxygen was shown to the oxygen preparation room and after being clothed in fiberglass clothing as described, was assisted into the chamber. Communications were checked and TV cameras were set in place. One-hundred per cent oxygen was admitted at line pressure (50 lb. per square inch) for a period of 2 minutes: this period was necessary to replace all of the air in the chamber with 100 per cent oxygen. When this was accomplished (by Beckman analyzer) the line pressure was readjusted so that oxygen inflow was slightly greater than outflow, and pressure was allowed to rise in the chamber at the rate of 2 pounds per minute to 29.4 pounds per square inch gauge. Since pure oxygen was sweeping through the chamber there was no accumulation of carbon dioxide. At this time, input and outflow were matched at the controls, the pressure remained stable and the "soaking" time of 30 minutes was begun. At 15 to 20 minutes into the "soaking" period, the chamber and patient were wheeled to the cobalt unit room and the patient was correctly positioned under the Picker cobalt machine. At precisely 30 minutes soaking time the patient was irradiated (Fig. 3). This procedure usually took approximately 2 minutes, after which the patient was returned to the oxygen preparation room and decompression initiated at the rate of 4 pounds per minute. The total cycle usually occupied 55 to 56 minutes.

## RESULTS

This randomized study had been underway for over 2 years. During this period 52

patients were treated and nearly 1,000 compressions completed, when the project was prematurely and violently terminated by an explosive decompression of the chamber (see article which follows). The decompression was caused by a rupture of the plastic material which propelled plastic projectiles over the entire cobalt unit room and left it in shambles (Fig. 4-7). Although both the patient and the senior author survived the accident, the project was not continued. Two years have now elapsed and despite the small numbers of patients involved, both authors feel that these results should be made known to those presently engaged in investigation in this field. Of the 52 patients admitted to the study, 3 patients under hyperbaric oxygen therapy at the time of the explosion did not have the complete course of oxygen and radiation therapy, and were thus not available for inclusion in the results. There remain 49 patients who satisfied the requirements of the protocol: 23 randomly assigned matched pairs and 3 patients who remained unmatched at the unexpected termination of the study. The over-all survival rates for the series (Table 1) showed that at the end of 1 year, 15 of 25 patients treated with hyperbaric oxygen as an adjunct to radiation therapy survived, and a similar number, 15 of 24 patients treated with radiation therapy alone survived. Two year survival rates were again comparable; i.e., 8 of 25 patients treated with hyperbaric oxygen survived as compared with 8 of 24 patients treated with radiation therapy alone. Survival rates of 2½ to 3 years again demonstrated similar survival: 7 of 25 patients in the hyperbaric oxygen group, and 5 of 24 patients who received radiation therapy alone. Thus, it can be said that no statistical difference was noted in the over-all survival rates in this series when hyperbaric oxygen was utilized as an adjunct to radiation therapy over radiation therapy alone. The question arises, did the survival rates give any contrary indications when approached in terms of location and extended disease? None has been demonstrated thus far.



Fig. 3.

## HEAD AND NECK

Seventeen patients in the head and neck series, divided into 8 matched pairs with 1 patient unmatched, demonstrated neoplasms in the base of tongue, valleculae, pyriform sinus and pharyngeal wall; 6 pairs of patients demonstrated far advanced disease (3 T<sub>4</sub>, No; 3 N<sub>3</sub>, Mo); 2 pairs of patients had advanced disease (1 T<sub>3</sub>, No; 1 T<sub>3</sub>, Mo).

At 1 year (Table II) 7 of 9 of the hyperbaric patients survived, compared with 5 of 8 patients treated with radiation alone. Two year survival figures were again comparable: 5 of 9 hyperbaric oxygen patients survived against 5 of 8 patients receiving radiation therapy alone. The  $2\frac{1}{2}$  to 3 year survival figures of 5 of 9 hyperbaric oxygen patients surviving against 4 of 8 patients







Fig. 5.



Fig. 6.

treated with radiation alone again did not present a significant difference in survival. When one inquires as to any differences in survival between those patients with advanced disease and those with far advanced disease, one would presume that the patients with far advanced disease had tumors which contained large clusters of hypoxic cells and might show better results in the hyperbaric series. At I and 2 year survival periods, 4 of 6 patients survived in both groups; 4 of 6 patients in the hyperbaric group demonstrating far advanced disease survived to the  $2\frac{1}{2}$  to 3 year periods, whereas 3 of 6 treated with radiation alone survived to  $2\frac{1}{2}$  to 3 years. This slight difference was not considered significant for this series.

## CERVIX

Fourteen patients in 7 randomly matched pairs were studied: 5 pairs had moderately

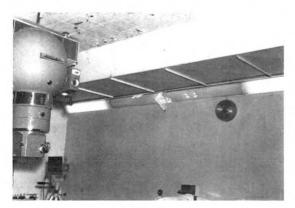


Fig. 7.

TABLE I
PATIENT OVER-ALL SURVIVAL RATE

Survival	1 Year	2 Years	At Risk
Hyperbaric O <sub>2</sub> and Radiation Therapy	15/25	8/25	7/25 (27-36 mo.)
Radiation Therapy Only	15/24	8/24	5/24 (31–36 mo.)

advanced disease, Stage IIIA and IIIB, and 2 pairs had far advanced disease, Stage IV. The I year survival figures for the hyperbaric group showed 4 of 7 patients surviving, compared to 6 of 7 treated with radiation alone, demonstrating no remarkable differences. The 2 year survival figures showed 3 of 7 hyperbaric patients surviving, compared to 4 of 7 treated with radiation alone. Again, no remarkable differences were evident, although both survival rates compared favorably with the series of Kline et al.11 recently completed at the University of Wisconsin. If one again considers survival of those patients with far advanced disease, Stage IV, at 2 years, 4 out of 6 patients survived in both series and at 2½ to 3 years, 4 of 6 hyperbaric patients survived compared with 3 out of 6 treated with radiation alone. While the survival figures of both groups are high, there is again no significant difference to be noted.

## BLADDER, RECTUM, BRAIN, ESOPHAGUS

The 6 patients in the bladder series, all Stage D disease, showed a 2 year survival figure of only I patient in the radiation therapy alone category. Four patients in the recurrent rectal cancer, Duke's C classification, showed only I survivor at I year in the group with radiation therapy alone and no survivors at 2 years. There were no survivors at 12 months of the 4 patients in the glioblastoma series. Of the 4 mid-third esophagus patients, with the methods under study, there is still I patient at risk at 31 months who was treated with oxygen as an adjunct. None of the other patients in the esophagus series survived past I year.

Table II
SURVIVAL RATE OF PATIENTS WITH CARCINOMA OF HEAD AND NECK

Survival	1 Year	2 Years	At Risk	Advanced	Far Advanced
Hyperbaric O <sub>2</sub> and Radiation Therapy	7/9	5/9	4/9	3/3	1/6
Radiation Therapy Only	5/8	5/8	2/8	1/2	1/6

Table III
SURVIVAL RATE OF PATIENTS WITH CARCINOMA OF CERVIX

Survival	1 Year	2 Years	At Risk	Advanced	Far Advanced
Hyperbaric O <sub>2</sub> and Radiation Therapy	4/7	3/7	2/7	2/5	0/2
Radiation Therapy Only	6/7	4/7	3/7	2/5	1/2

 $\begin{tabular}{ll} $T$ able $IV$ \\ $survival $\ rate of patients with malignancy of bladder, \\ $rectum, brain and esophagus \\ \end{tabular}$ 

Survival	Bladder	Rectum	Brain	Esophagus
1 Year Hyperbaric O2 and Radiation Therapy	1/3	0/2	0/2	2/2
1 Year Radiation Therapy Alone	2/3	1/2	0/2	1/2
2 Years Hyperbaric O <sub>2</sub> and Radiation Therapy	0/3	0/2	_	At Risk
2 Years Radiation Therapy Alone	1/3	0/2		0/2

## DISCUSSION

One of the striking aspects of this series was the willingness of the patients, no matter what their age (36 to 74 years), intellect or emotional content, to undergo this complex series of treatments. All patients in the series, including the glioblastoma, tolerated the hyperbaric oxygen experience well, and no convulsions were noted in nearly 1,000 compressions. A series of electroencephalograms taken immediately prior to and following compressions

of the glioblastoma patients did not demonstrate any convulsive prodrome. No cardiac difficulties were encountered, although many of the patients submitted to as many as 35 compressions in their respective series. Nausea was controlled with compazine and no episodes of emesis were encountered while the patients were in the chamber. No compromises were necessitated by the chamber presence in the execution of exact patient set-up under the cobalt 60 machine. In the post-treatment period, none of the patients

developed transverse myelitis, and no body necrosis was visualized by direct or roentgenographic examination. No persistent diarrhea or severely contracted bladder histories were obtained.

The use of daily fractionation was an integral part of the study from its inception for the reasons previously stated. Statistically, it was of the utmost importance that there be only one principal variable in the study. Was Henry Kaplan years ahead when he stated in San Francisco in 1965?, "Fractionation is the poor man's oxygen chamber."

### SUMMARY

In order to more comprehensively evaluate the potential of the oxygen effect in patients with advanced neoplastic disease of the head and neck, cervix, bladder, rectum, esophagus and brain, a randomized series was designed to test the efficacy of hyperbaric oxygen as an adjunct to radiation therapy as compared to radiation therapy alone. One-half of the patients admitted to this study of the theoretic potentials of hyperbaric oxygen received 100 per cent oxygen under 3 atmospheres absolute pressure as an adjunct to regularly fractionated daily radiation therapy. The other half received daily radiation therapy alone.

This study was terminated prematurely by accidental explosive decompression and destruction of the chamber on the 52nd patient admitted to the series.

Twelve of the original 52 patients remain at risk, 27 to 36 months. These patients are equally divided between the 2 modalities.

There were no significant differences in survival noted in any of the anatomic areas of advanced neoplasms in the randomized series of daily radiation therapy with hyperbaric oxygen as an adjunct compared to the radiation therapy alone series.

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# EXPLOSIVE DECOMPRESSION IN A HYPERBARIC OXYGEN CHAMBER

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THE explosions that caused the death of three astronauts on the launching pad at Cape Canaveral in 1967, and a few weeks later killed two corpsmen at Brooks Army General Hospital in Texas, sharply focused the eyes of the medical world on the potentials for danger in research with hyperbaric oxygen.

These potentials were well-known to the medical investigators utilizing pure oxygen under pressure in their research. Investigators such as Churchill-Davidson, van den Brenk and Wildermuth, mindful of the dangers, have over the years incorporated preventive measures in their protocols, specifically designed to minimize the possibility of explosion by careful attention to equipment design and patient manipulation in the atmosphere of pure oxygen under increased pressure.

The protocol for investigation of hyperbaric oxygen as an adjunct to radiation therapy in the treatment of neoplastic disease at the University of Wisconsin specified the same careful attention to detail for the chamber and its ancillary equipment.

Patients to whom this adjunctive therapy was offered were those whose tumors were far advanced: usually large sized neoplasms of the brain, head and neck, esophagus, cervix, bladder and rectum. Randomization was made between daily fractionated radiation therapy alone and oxygen as an adjunct to daily radiation therapy. All patients were to be subjected to 3 atmospheres absolute pressure (2 atmospheres, 29.4 lb. gauge) for a minimum period of 15 minutes at full pressure to ensure maximum oxygen diffusion to the hypoxic cells more than 150 micra from their blood supply in the tumor cord at the moment of irradiation. The pa-

tients were limited to a maximum of 58 minutes total cycle to avoid any potential for oxygen toxicity, known to manifest itself after over 1 hour exposure to 100 per cent oxygen under 3 atmospheres absolute pressure

Because the radiation source to be utilized in the treatment was a cobalt 60 unit, employing the C arm principle with the large counter weight acting as a shield, the usual 4 legged chamber could not be utilized. A cantilevered type chamber was then used which fits over the counter weight and under the cobalt source with ease.

The technique used in pressurization of the chamber, irradiation of the patient and decompression is described in the preceding article.

On May 2, 1968, the 6th patient of the day, appropriately dressed in fiberglass gown and dampened surgical cap, was placed on the couch and inserted into the chamber. This patient, 60 years of age, had an advanced bladder cancer and had been randomized to receive hyperbaric oxygen utilizing 200 rads tumor dose daily for 5 days per week. He had become acclimated to the procedure over the two preceding weeks of combined therapy and had little anxiety toward the cycle of treatment. The door to the chamber was closed, the interior and TV systems were checked and found operational, and the first stage of the cycle was initiated. Pure oxygen was admitted to the chamber for a period of 2 minutes and the air content was thus washed out. The pressurization of the chamber with pure oxygen was started, the rate of induction being a raise of 2 lb./min. or 14.5 minutes to raise the pressure to 29.4 lb. gauge or 3 atmospheres absolute. During this period the patient chewed gum, thus adjusting to

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the increasing pressure in the middle ear. When the full 3 atmospheres absolute pressure was obtained, no further compensation was needed. The soak period of 15 minutes was begun and the chamber, with patient, was then moved from the preparation room to the Co<sup>60</sup> radiation room at 29 minutes into the cycle. The process of patient set-up was in progress when the explosive decompression occurred. The plastic portion of the chamber had spontaneously ruptured, permitting explosive decompression of the patient in the chamber and propelling large chunks of plastic with projectile velocity around the cobalt unit room.

At that point in time, 4 persons were involved in the operation: the patient, the research director, the hyperbaric technician and the radiation technician.

The hyperbaric technician, seated at the control console of the chamber observing via TV and listening to the patient in the Co<sup>60</sup> treatment room, heard the explosion and reacted according to the preplanned and often rehearsed emergency procedure and immediately closed off the main oxygen supply. She, of course, was not injured.

The radiation technician, standing some distance back from the chamber observing the set-up procedure of the doctor, followed the emergency procedure and went immediately to the patient. Since the plastic exploded, only powdery fragments of plastic fell on the patient and no serious surface injuries were noted at that time. After removing the patient from the ruptured chamber, he was placed on a mobile stretcher and removed to the hall where other staff radiologists examined him. The radiation technician was found to have incurred a laceration over the forehead.

The research director was noted lying 8 feet from the chamber in an unconscious state and the "Blue Cart" team (an emergency cardiac resuscitation team of the University Hospital) was called for. Upon their arrival, I had already regained consciousness and asked about the patient.

At this point in time, the patient was noted to have some dyspnea and was

wheeled into a nearby diagnostic radiologic room by the "Blue Cart" team of physicians. A bilateral hemopneumothorax was visualized on fluoroscopy and immediate tubing of the patient by this specialized team relieved the pneumothorax. The patient was able to re-initiate radiation therapy in 10 days.

The Co<sup>60</sup> source, never having been exposed, was safe. Although fluorescent tubing all around the room was ruptured exposing the glowing filaments, the dilution factor of the confined oxygen was apparently sufficient to bypass any explosion. The research director was at the moment of explosion bending over the plastic portion of the chamber, setting up the Co<sup>60</sup> field, and received the full force of the exploding plastic on his mandible and was thrown back across the room to a threepoint landing. His head hit a steel bookcase used to hold the Co60 lead blocks and his back and elbow hit the concrete floor. Injuries sustained included multiple mandibular fractures, lumbar and left shoulder injuries, and extensive facial lacerations.

The Co60 unit room was a shambles, with all areas demonstrating the effects of flying particles of plastic. The Picker Co60 unit survived the explosion with but a few scratches on its almost impregnable surfaces. Its rotation capacity was not compromised and the light and mirror, protected by the collimator, were intact. Air-conditioning ducts located on the ceiling and fluorescent light fixtures ringing the ceiling were torn off, indented and the tubing ruptured. The sound-proofing material in the ceiling also demonstrated the force of the flying particles. Since the control console for the chamber was in the preparation room, separated from the cobalt unit room by concrete walls and a 2 ton concrete and steel door, no damage was possible, and the often-repeated emergency procedures were executed with precision and dispatch by all concerned. This certainly prevented the major possible catastrophe of oxygen fire with its extremely rapid and widespread devastation to people in the area.

In retrospect, the time devoted in the initial planning stages of the investigation, to accident and fire prevention was invaluable. There is little doubt that failure to consider the sources of static electricity and lack of precise and adequate emergency procedures on our part would have resulted in much more damage and fatal injuries to

the persons involved. With these precautions, some compromise with the potentials for danger in hyperbaric research was made.

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# A PASSIVE TREATMENT VERIFICATION DEVICE\*

By EARL VAN ROOSENBEEK and THOMAS G. NELSON HOUSTON, TEXAS

HE many current models of megavoltage radiotherapy equipment offer a wide range of treatment parameters. There is a choice of electron or photon beams, variable energies, and almost infinite combinations of field sizes, beam filters, and flatteners. When all variables are incorporated into one machine, the possibility of an error in patient treatment is greatly increased. To reduce this possibility on an 18 mev. betatron, a passive treatment verification device has been built and installed. This device is inactive, as opposed to the punch card or tape devices used to automate patient set-up. It is designed around a card translator which "reads" a prepunched card and verifies that at least 4 of 6 sets of variables have been correctly set. These are:

		Choice of
1.	Beam mode, photon or electron	2
2.	Energy: 6, 9, 12, 15, 18 mev.	5
3.	Electron filters, 0 to 9	10

4. Photon compensators: none,
No. 1 or No. 2

Total variables

20

An error in setting in this group of variables could mean a large difference in dose delivered to the patient.

Among the variables not verified by the card reader are field size, distance, and head and cone angle. These are a very obvious part of the visual set-up of the patient. The treatment end of the field size cone fixes the distance, and the field size and angle must correspond to an area drawn in ink on the patient's skin. An error in this part of the treatment is less likely to occur and would introduce considerably less error in dose delivered than the factors listed above.

Figure 1 shows the card reader, card and punch unit on the betatron console. A blank card is placed in the punch unit and the 4 variables are punched. The card is

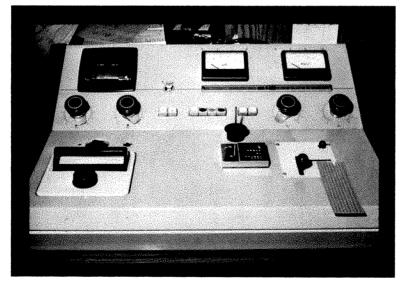


Fig. 1. An 18 mev. betatron control console showing card punch, card and reader.

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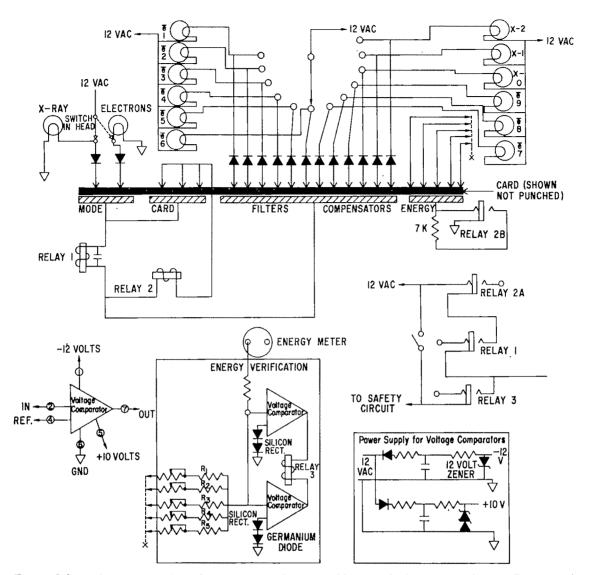


Fig. 2. Schematic representation of card reader. The 5 variable controls, in a series of R1 to R5, control the bias voltage for the 5 energies. They can be set to allow operation at only the exact energy or up to ±1 mev.

inserted into the reader and a manual lever is moved forward (black knob). If the parameters have been correctly set as indicated on the panel (lights and meters), the machine can be turned on. The card is filed in the patient's treatment chart and inserted into the reader before each treatment.

Figure 2 is a schematic representation of the verification device. The card reader was salvaged from an electron tube tester. Spring-loaded pins make electrical contact through the punched holes. Treatment parameters are illuminated on the betatron panel or indicated on a panel meter. The voltage present on these key-indicated points is used to activate relays through the pin contacts and the properly punched hole. Unless a properly punched, undamaged card is in place in the reader, the betatron cannot be energized. The energy verification circuit is composed of 2 voltage comparators which read the voltage from the energy meter through a voltage divider

network which is determined by the punched card and compared to a fixed bias. A switch electrically removes the verification unit from the betatron for nontherapeutic use.

### SUMMARY

The critical variables in individual patient treatment are verified by placing a prepunched card in a translating device. A simple go-no-go circuit prevents the treatment from proceeding if any 1 of 4

groups of variables have been set incorrectly. This device could be adapted for use in other therapy equipment in which large numbers of variables pose a potential problem.

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# A NEW METHOD TO DETERMINE THE FOCAL SPOT SIZE OF X-RAY TUBES\*

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NE of the most important causes of the loss of resolution in an x-ray imaging system is the finite size and shape of the x-ray focal spot. A knowledge of the limitations imposed by focal spot size is particularly important when one attempts to improve upon resolution by the adoption of such techniques as direct magnification.<sup>3,8</sup> The size of an x-ray focal spot is traditionally estimated by making a pin-hole image of it at some convenient magnification. 5,6 Recently, Friedman and Greenspan<sup>2</sup> have suggested an alternate method based on the imaging of fine wires. As pointed out by these authors, pin-hole as well as wire images are usually blurred and unsharp at the edges, thus making the measurement of focal spot dimensions difficult and somewhat arbitrary. Furthermore, the estimated dimensions are also influenced by the exposure technique employed in making these images (Fig. 1). In a recent communication,10 we suggested a more accurate method based on the experimental measurement of the modulation transfer functions (MTF) of x-ray focal spots. Measurement of these functions, however, involves very careful experimentation as well as the use of an electronic digital computer.11

In this communication, we wish to propose a method based on the phenomenon

of spurious resolution of periodic patterns, often referred to in the literature<sup>4,7</sup> but never before used in a practical way.

#### THEORY

Morgan<sup>9</sup> has shown that the sine-wave response or the modulation transfer function of an x-ray focal spot of size a is given by the equation:

$$M(f) = \frac{\sin \pi f a d_2 / (d_1 + d_2)}{\pi f a d_2 / (d_1 + d_2)} = \frac{\sin \theta}{\theta}, \quad (1)$$

where M(f) is the modulation transfer function and f is the spatial frequency (lines per mm.) of a test object of sinusoidal transmission placed at a distance  $d_1$  from the focal spot and a distance  $d_2$  from the film;  $\theta$  is the quantity  $\pi f a d_2/(d_1+d_2)$ .

Coltman<sup>1</sup> has shown that the square wave response function S(f) of an imaging system is related to its modulation transfer function M(f) through the equation:

$$S(f) = \frac{4}{\pi} \left[ M(f) - \frac{M(3f)}{3} + \frac{M(5f)}{5} - \frac{M(7f)}{7} + \frac{M(9f)}{9} - \cdots \right].$$
 (2)

Substituting Equation (2) in Equation (1) we get:



Fig. 1. Diagram illustrating the influence of exposure factors on the estimation of focal spot size by the pinhole method. The images shown here were made at various mas, values.

<sup>\*</sup> From the Department of Radiology, The Johns Hopkins University and Hospital, Baltimore, Maryland.

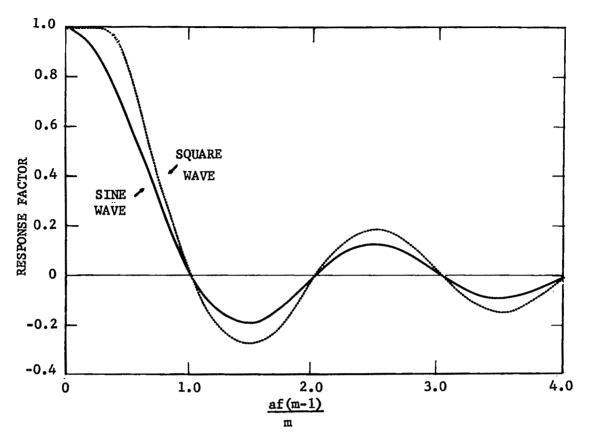


Fig. 2. The modulation transfer function (MTF) and the square wave response of a focal spot of size a f is the spatial frequency and m is the magnification factor.

$$S(f) = \frac{4}{\pi} \left[ \frac{\sin \theta}{\theta} - \frac{1}{3} \frac{\sin (3\theta)}{3\theta} + \frac{1}{5} \frac{\sin (5\theta)}{5\theta} - \frac{1}{7} \frac{\sin (7\theta)}{7\theta} + \frac{1}{9} \frac{\sin (9\theta)}{9\theta} \cdots \right].$$
(3)

From Equations 1 and 3, it follows that when  $\theta = \pi$ , M(f) and S(f) are each equal to zero. In other words, the sine wave response and the square wave response are both equal to zero when the spatial frequency f reaches a certain critical value satisfied by the equation:

$$\frac{af d_2}{(d_1 + d_2)} = 1$$
 or  $\frac{af(m-1)}{m} = 1$ , (4)

where m represents the magnification ratio  $(d_1+d_2)/d_1$ . Further increase of the spatial

frequency results in negative values for the MTF and the square wave response (Fig. 2). Alternately, if one were to obtain a series of progressively magnified radiographic images of a bar pattern of a given spatial frequency f using an x-ray tube with a focal spot of given size a, the pattern will just disappear at some critical value of m, given by the equation:

$$m = \frac{af}{af - 1}$$
 or  $a = \frac{m}{f(m - 1)}$ . (5)

Further increase of *m* causes the pattern to appear again but with a reversal of the dark and bright areas, because of the negative values for the square wave response. This reappearance of the pattern is referred to as spurious resolution, for it occurs only when periodic patterns are imaged. Knowing the magnification factor for the film in

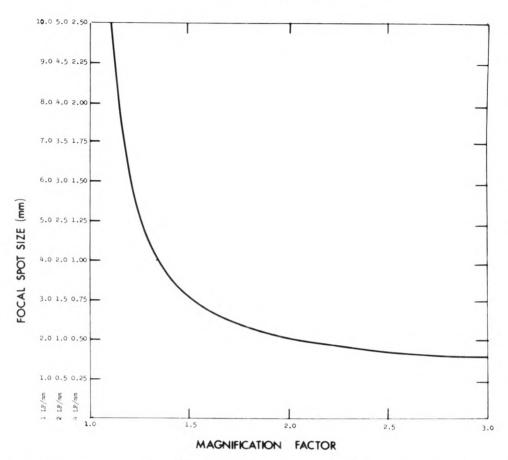


Fig. 3. Diagram showing the relationship between focal spot size and the critical magnification factor at which the contrast in a roentgenogram of a bar pattern of a given spatial frequency reaches its lowest value.

which the pattern just disappears and the spatial frequency of the bar pattern used, the size of the focal spot can be determined precisely using Equation 5 or its graphic equivalent shown in Figure 3.

## EXPERIMENTAL PROCEDURE

The validity of the above procedure has been confirmed experimentally as follows.

A test-object (Fig. 4) consisting of a bar pattern and 2 small pieces of platinum wire separated by a distance of 5 cm. was roent-genographed several times, placing it progressively at varying distances from the film. The focus-film distance was 100 cm. A non-screen film was used without intensifying screens to ensure that no significant part of the blurring was caused by factors

other than the focal spot size. Care was taken to ensure that the bar-pattern was always held perpendicular to the anodecathode axis of the tube and that it was moved strictly along the central axis of the

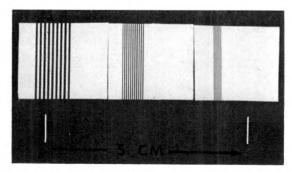


Fig. 4. Test object used for making roentgenograms at varying magnification factors.

beam. These precautions were important as the size of a focal spot is not the same in all directions; furthermore, it varies considerably with the angle of projection with respect to the central axis.

The magnification factor for each of the roentgenograms thus made was obtained by measuring the distance between the images of the 2 platinum wires and dividing it by 5 cm., which was the original distance between them. The film in which the pattern just disappeared was ascertained as carefully as possible by visual inspection. Knowing the magnification factor for this critical film, the effective focal spot size was calculated using Equation 5. Figure 5 shows the various roentgenographic images obtained with bar patterns of spatial frequencies of 1 line pair/mm., 2 line pairs/

mm. and 4 line pairs/mm., respectively. Notice the precision with which it is possible to ascertain the critical film in each case.

Table I shows a summary of our measurements with 3 different x-ray tubes. Notice that in each case, the estimates made by the null method described in this paper are closely in agreement with those obtained by a direct experimental determination of the modulation transfer function. The details of this second method have been published elsewhere.<sup>10</sup>

## CONCLUSION

A method is described to determine the effective dimensions of x-ray focal spots, making use of the phenomenon of spurious resolution that occurs when periodic pat-

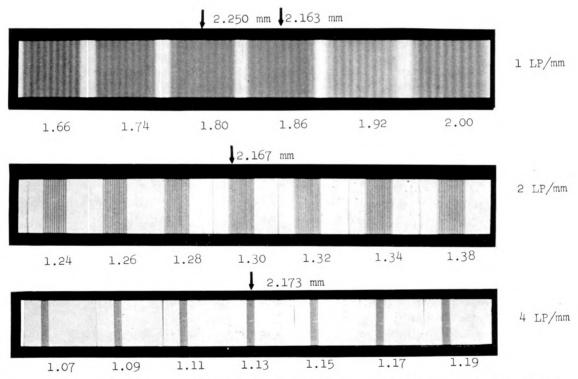


Fig. 5. Roentgenographic images of bar patterns of I line pair/mm., 2 line pairs/mm. and 4 line pairs/mm. at various magnification factors. The number below each roentgenogram represents the corresponding magnification factor. The critical film in each case is marked by an arrow. To the right of the arrow is the focal spot size calculated from a knowledge of the magnification factor corresponding to the critical film.

Note that as one moves from left to right, the resolution progressively deteriorates until it becomes minimum at the critical magnification factor. Moving further to the right, the resolution improves again but with a reversal of the dark and bright regions.

 $T_{\rm ABLE}\ I$  focal spot dimensions of 3 different X-ray tubes measured along the central axis of the beam

	Parallel t	o the Anode-Ca	thode Axis	Perpendicular to the Anode-Cathode Axis			
	Manufac- turer's Value	Method Based on Measurement of the MTI <sup>710</sup>	Null Method Based on Observance of Spurious Resolution	Manufac- turer's Value	Method Based on Measurement of the MTF <sup>10</sup>	Null Method Based on Observance of Spurious Resolution	
Tube 1	mm.	mm.	mm.	mm.	mm.	mm.	
(small focal spot)	1.0	1.5	1.54	1.0	1.4	1.39	
Tube 1 (large focal spot)	2.0	2.1	2.14	2.0	2.5	2.51	
Tube 2 (small focal spot)	1.5	1.4	1.38	O. I	1.6	1.57	
Tube 2 (large focal spot)	2.0	2.9	2.92	2.0	3.1	3.17	
Tube 3 (small focal spot)	0.5	0.7	0.68	0.5	0.6	0.64	
Tube 3 (large focal spot)	1.5	1.8	1.94	1.5	1.9	1.95	

MTF = Modulation transfer function.

terns are imaged. The main attraction of this method is that it is based on the observance of a type of "null" effect rather than direct measurement. For this reason, errors inherent in the traditional pin-hole method are largely avoided. These include dependence of measured size on the density of the image, the size of the pin-hole, the thickness of the lead plate in which the pin-hole is made, absorption effects in the pin-hole, etc. Although the practical realization of the null method described here is quite simple, great care must be exercised to ensure the positioning of the test-pattern strictly along the central axis of the x-ray beam, with the line pairs either strictly parallel or strictly perpendicular to the anode-cathode axis of the tube. In directions other than these, the phenomenon of spurious resolution may not occur for reasons discussed in detail elsewhere.10

### SUMMARY

A method to determine the focal spot size of x-ray tubes is described. The method is based on the observance of the critical magnification factor at which the contrast in a roentgenogram of a periodic barpattern of known spatial frequency reaches its minimum value before increasing again with a reversal of the bright and dark areas.

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# M E D I T O R I A L S M

# INEFFICIENT USE OF X RAYS IN DIAGNOSTIC RADIOLOGY\*

THESE remarks will be directed, in the main, to calling attention to some of the practical penalties that may be brought about through the improper or inefficient use of x rays in diagnostic radiology. Except for 3 or 4 instances, which I shall mention briefly, the results of improved procedures and techniques can be expected to pay only relatively small dividends in terms of patient exposure. This is not to suggest that one should ignore them, but it is to point out that there are certain areas upon which attention should be concentrated.

The profession has been warned many times about the problems which are being brought out and grossly exaggerated today in public forums by individuals relatively lacking in knowledge about radiologic problems, and under circumstances where an objective technologic evaluation of the problem is not really feasible. It should not have to be pointed out that the understanding of a need for the protection of patients against deleterious effects of radiation is hardly new. Within 4 or 5 months of the discovery of x rays, skin damage was noted and the first steps taken to limit radiation exposure. Especially in the last few decades the obvious and enormous benefits to be obtained from radiation in medicine became more evident day by day and demands for radiation use are still increasing steadily. Thus in the consideration of protective measures there has been from the very outset, the necessity for achieving some kind of balance between exposure of the patient, exposure of the operator, shielding of the tube, limiting the beam and so on.

But no more today than 75 years ago, is it possible to arrive at a perfect technologic balance among such diverse factors; human or medical factors which cannot be made quantitative will always be involved. The final answers in achieving irradiation efficiency will involve the exercise of technologic judgment and skills by the manufacturers and designers as well as medical judgment by the physicians.

Efficiency in the diagnostic use of x rays can be defined in a number of ways, but since it cannot be measured in an absolute sense, it may be thought of in more general terms—such as the obtaining of a maximum amount of medical information, for a minimum amount of total radiation exposure of a patient. It is not necessarily possible to reduce radiation exposure to any absolute minimum. Judgment must intervene.

Judgment is what separates the men from the machines, and it is involved in nearly every step of radiologic practice. Highly qualified judgment must be applied in determining the extent to which a patient is exposed in terms of the information that is to be obtained—or whether the procedure should be carried out at all. Only highly qualified judgment can evaluate the possible harm of any necessary or unnecessary radiation exposure to the patient (or to the population) or the value to the patient of the information obtained. The physician must supply these judgment values.

Any step directed to improvement of radiation efficiency may carry some counter effect, but there are one or two notable

<sup>\*</sup> Presented at the Seventy-first Annual Meeting of the American Roentgen Ray Society, Miami Beach, Florida, September 29-October 2, 1970.

exceptions. The counter effect may show in the loss of some degree of flexibility or loss of information which in turn may adversely influence a medical procedure. While it is very easy to enumerate a vast number of factors which can be said to improve irradiation efficiency, it is not at all certain that these can be applied individually without relationship to any of the others.

Why review all of this now? The main reason is to emphasize that the problems are not new, nor are they mysterious. They have not been neglected—they are still being investigated. We still hear talk about needing faster x-ray film, faster intensifying screens, more shielding, less exposure time, better defined fields and so on. These are all real problems and they have always been real problems. But whereas in the past we have been able to improve these by factors of tens or hundreds, we have now so advanced our technology that future improvements will be by twos or threes at most. There may be still room for some improvement, but it will come slowly, be less notable, and cost more. And, it might be added, some of what is presented as significant improvement may well be little more than number juggling, and may be of academic interest without any practical application.

It must be pointed out that while for at least 3 or 4 decades protection of the patient was second order to protection of the physician or radiologist, concern over the patient has not been neglected. Attention was directed to this problem in the very first report of the National Council on Radiation Protection and Measurements (NCRP) that was issued in 1931, and it has recurred with increasing emphasis in each of the 6 successive editions on medical x-ray protection that have been produced since then. Part of the reason for this redirection of emphasis was the fact that the potential long-range effects of radiation exposure did not begin to be understood and appreciated in perspective until about 1950, although there was a qualitative

understanding of the concept many years before that. A second reason was the fact that, whereas the individual patient is only exposed occasionally, the physician and the technician are subjected to repeated exposures and hence patently much larger total doses of radiation.

The role of the NCRP has been continuous in the furtherance of medical x-ray protective philosophy and procedures. This organization, formed as a Committee in 1929, initially consisted of representatives from the several radiologic societies and the x-ray industry; in essence it was the consolidation of all of the radiation protection committee activities then scattered among a number of organizations in the United States. In the medical area alone it has produced 7 reports over the years and this has essentially provided the backbone for all national and international guidance in the field.

As already noted, the attention directed to patient protection has increased steadily as the revisions have occurred. There is no question that this program, joined in by many radiologists and allied scientists, has worked and worked well and accomplished a great deal, but it must also be patently obvious that it has not worked well enough. Had the medical profession, by and large, followed the recommendations of these reports over the past 40 years, there would have been absolutely no grounds for some of the recent criticisms that have been directed toward the medical profession in its uses of radiation.

The NCRP has also drawn special attention to the problem of patient exposure following the studies by various genetics groups in 1956 at which time the fallout from nuclear weapons testing was very much on everyone's mind. As it turned out, the genetically significant dose from nuclear weapon fallout was much smaller than expected, but in the process they found that the genetically significant dose from medical procedures was apparently much larger than was expected. The origi-

nal rough surveys of medical exposure at that time led to an average genetically significant dose to our population that was something of the order of 100 times higher than it was later found to be through a sophisticated survey by the Public Health Service in 1964. But the 1956 study developed a level of alarm which does not seem to have abated at all in proportion to the more nearly correct average population dose established later.

The survey by the Public Health Service, in addition to arriving at an average genetically significant dose of 55 millirems per year, also determined that there were numerous faults in the way x-ray equipment was either constructed, or operated, or both. The biggest single source of avoidable exposure of the patient was due to excessively large field sizes in relation to the size of film used. They have made a rough estimate that, if in all cases of diagnostic radiography the x-ray field on the patient was no greater than was necessary to cover the film, the genetically significant dose could have been reduced to onethird of its present value.

The only comment on this, is that it is an undesirable fact. Moreover it is easily correctable at little or no cost. It is continuance of some of this kind of poor practice that opens the medical profession to attack with enough basis so as to make much less important items appear equally important in the eyes of the public.

Probably of appreciable importance is the question of film-processing techniques and procedures. Here the difficulty lies much more in the offices of the nonradiologists than the radiologists. This situation has been pointed out frequently and has also been emphasized by the NCRP. It, of course, centers around the fact that where inadequate film processing procedures are used, the films are often over-exposed and underdeveloped, and at times even repeated; of course, both of these actions contribute to unnecessary exposure of the patient.

The selection of "film speed" is a point frequently brought out by critics of medical x-ray practice, but here is a place clearly where technical achievement has certain limitations and final selections of film must be decided by competent clinical judgment. Reduction of radiographic exposure is generally accomplished (other things being equal) by a fast combination of film and intensifying screen. Available film speeds today are very much greater than even a few years ago, but if the combination of film-screen speed is pushed to the limit there will be a loss of definition through increased "graininess" (quantum mottle). Depending upon the particular diagnostic procedure, use of the fastest film-screen combinations might result in obscuring radiographic evidence of the condition under examination. Therefore this becomes a problem of judgment for which there is no universal solution.

Another means for reducing patient exposure that is talked about with more glibness than knowledge is the use of gonad shields. There are certain conditions under which the testes or ovaries may be shielded easily without interfering with the diagnostic results. But there are many cases where the dose is likely to be substantial yet where shielding of any kind is impractical.

If substantial attention were paid to the field size and diaphragming, such as mentioned above, together with strict alignment of the beam to the region of examination, there would be relatively small gain through the use of gonad shields. So long as the gonads are outside of a direct beam there is no shielding that will importantly reduce the scattered radiation.

The fact that some of our radiologic practices have been sufficiently poor over recent years and so obvious even to inexperienced people, has led to demands for legislation and regulations to control radiation. In addition to being out of proportion to the other normal risks to which man is exposed, regulatory actions may, if not

carefully watched, lead to a deterioration of some of our medical care as well as greatly increased cost, and hence it may reduce some of its availability.

The 1964 survey made by the Bureau of Radiological Health showed that some 100,000,000 diagnostic x-ray studies are made in each year, covering everything from simple fracture examinations to the most elaborate visualization of the brain arteries. This means that on the average about half of our population has a diagnostic examination involving radiology each year.

It is against this backdrop that there should be some examination of the way "numbers games" are coming into use as a means of influencing public or special groups on radiation matters. An excellent example has occurred in connection with the Congressional Hearings on a Bill to promote a "Radiation Control for Health and Safety Act of 1967." This is an act supported in principle, if not in detail, by most knowledgeable organizations and individuals. Nevertheless, considerable encouragement and great publicity was given to some statements, purporting to be based on scientific and clinical evidence, but, instead, based largely on assumptions, extrapolations and dubious calculations that have limited relation to established facts and serve little purpose other than to confuse the public. A random example may be quoted:

"There is no question that the use of diagnostic x rays saves many thousands of lives each year. No figures are available to give a reasonable estimate of the number of lives saved by this important diagnostic tool. However, to illustrate what I think should be our objectives, let us assume that in the present use of diagnostic x rays 100,000 lives are saved each year in the United States, and, as a result of unnecessary exposure, 30,000 lives are lost owing to an increase in malignancies and genetic damage and other causes.

"Our goal, and one which I think could be

attained, would be to double the lives saved and reduce by a factor of 10 the number of lives lost: namely to change this picture so that the use of x rays would save 200,000 lives each year and the number lost would be reduced to 3,000 or an additional saving of almost 130,000 per year."

It should be emphasized that such numbers are not based on any survey or statistical analyses. The existence of any data upon which to base any such numbers is not known, and there is serious doubt that it would even be feasible to try to carry out the studies needed to derive them. They are just a few of the numbers which have been bandied around and which have almost no scientific substantiation.

It has been said that the three medical miracles of the century which have most changed the health picture of our population would have to be antibiotics, public health and diagnostic radiology. To needlessly deprive one's self of x-ray diagnosis by virtue of the exercise of nonmedical judgment must be compared with individual failure to use the antibiotics prescribed by a physician to combat a serious infection.

The real situation must be viewed in such terms that if, because of overcaution in x-ray diagnosis today, the patient does not live beyond tomorrow, any question of long-range effects becomes academic the day after tomorrow.

In closing it should be pointed out that attacks on the medical profession, such as in some popular magazines or at some congressional hearings, serve to bring a problem before the public in a manner which the authors justify on the basis that it is the only course left available to them, however sensational and exaggerated it may be. In a limited sense they are right, because the medical profession has had these facts before them for many years and have not taken maximum advantage of them. Were the medical x-ray house in

completely good order, these attacks would not have been possible.

The most worrisome part is the justifiable fear that these sensational attacks will have and the dangerous effect of frightening people away from having needed radiation procedures when the risk from not having the procedure is vastly greater than

from having it—even under the worst conditions imaginable.

LAURISTON S. TAYLOR, Ph.D.

National Council on Radiation Protection and Measurements 4201 Connecticut Avenue, N.W., Suite 402 Washington, D.C.





HERBERT MILTON STAUFFER, M.D. 1914–1970

DR. HERBERT MILTON STAUF-FER, Professor and Chairman of the Department of Radiology at Temple University Health Sciences Center, died suddenly at his home on December 18, 1970.

Dr. Stauffer was born in Philadelphia on April 26, 1914, the son of Dr. Milton F. Stauffer and Anna Hood Stauffer. He was entirely a product of Temple University, receiving his Bachelor of Arts degree in 1935, M.D. in 1939, and M.Sc. in 1945, after 2 years of internship and 3 years of

residency training in radiology at Temple University Hospital.

During World War II he was a Lieutenant in the Medical Corps of the United States Naval Reserve and was radiologist at the Naval Base in Argentia, Newfoundland. While there, he conducted a fluoroscopic survey of the civilian employees of the base for tuberculosis.

Following the war, he was Assistant Professor of Radiology at the University of Minnesota from 1946 to 1949 and then returned to Temple University as Associate Professor of Radiology in 1949. He was made Professor in 1952.

More than 100 publications on various aspects of radiology are authored by Dr. Stauffer. He had an early interest in neuroradiology and was one of the first to apply catheter techniques for the visualization of cardiovascular structures. He pioneered in the design of television techniques to radiology and designed the first practical television stereoscopic fluoroscope. He is also responsible for a system of biplane high speed cineangiographic devices to study patterns of blood flow through the large vessels.

To implement his work, he organized a Radiology-Physiology laboratory which brought together clinicians and basic scientists and was one of the country's outstanding laboratories. The Department of Radiology at Temple University became the center of learning for advanced radiologic techniques and methods of education in academic radiology for clinicians, scholars,

and scientists in radiology from the Scandinavian countries, Western Europe, Australia and the Orient.

He was a Diplomate of the American Board of Radiology (1945) and a Fellow of the American College of Radiology (1954). In 1963 he was President of the Association of University Radiologists and in 1966 Chairman of the Executive Council of the American Roentgen Ray Society. In 1959 he was President of the Philadelphia Roentgen Ray Society and at his death he was President Elect of the Radiologic Society of North America.

Dr. Stauffer lived at Penn Valley, near Philadelphia, and is survived by his wife, the former Joan Dunbar, his son, Scott, and his sister, Mrs. Jo Stauffer Mullen, New York City.

Frederick Murtagh, M.D.

Professor of Neurosurgery Temple University, Health Sciences Center School of Medicine and Hospital Philadelphia, Pennsylvania 19140



# NATIONAL COUNCIL ON RADIATION PROTECTION AND MEASUREMENTS (NCRP)

THE NCRP (National Council on Radiation Protection and Measurements) during the last half of 1970 issued 2 important additional reports on recommendations for protection against radiation: Report No. 36; and Report No. 37.

NCRP Report No. 36, issued on August 15, 1970, is titled Radiation Protection in Veterinary Medicine.

This report represents some deviation from previous NCRP (National Committee on Radiation Protection and Measurements) practice in dealing with the subject. In the past, the NCRP has treated comprehensively in one report the use of x-ray sources in all medical applications (NCRP Report No. 26, National Bureau of Standards Handbook 76), and in another report the use of gamma-ray sources (NCRP Report No. 24, National Bureau of Standards Handbook 73). Each of these reports dealt with equipment design, the use of sources, patient protection and structural shielding. Subsequently, the Council decided that more useful reports would result from the consideration of equipment design and operational problems in one report and a separate consideration of structural shielding problems in another report.

NCRP Report No. 33, issued February 1, 1968, covers the design and the operational aspects of medical x-ray and gamma-ray equipment including protection of the patient. Report No. 34, issued March 2, 1970, covers structural shielding design for all types of x-ray and gamma-ray apparatus operating at energies up to 10 mev. Each of these reports includes, in considerable detail, recommendations relating to virtually all phases of the purposeful application of radiation in medical practice.

For specific veterinary applications, however, the Council decided to formulate one report dealing with both aspects of the problem. Thus, this report is concerned with both the design and operational aspects of veterinary radiation equipment, and matters relating to structural shielding design. While much of this material is already contained in Reports 33 and 34, this report presents the pertinent information which is applicable to the veterinary use of radiation. The NCRP believes that it is important for each radiation user in veterinary practice to be thoroughly familiar with the pertinent recommendations. If these remained embedded in the more comprehensive recommendations covering the whole radiation field, the availability of the information and its usefulness to the veterinarian would be somewhat limited.

This report is intended to serve as a guide to good practice. It provides basic standards which may be used in the preparation of regulatory protection codes but is not specifically written for literal adoption as legal regulations. Radiation sources discussed in this report may be subject to regulation by Federal, State or local governmental agencies. Such regulations may involve registration, licensing or compliance with specific rules.

The present report was prepared by the Council's Scientific Committee 17 on Veterinary X-Ray Protection. Serving on the Committee during the preparation of this report were: B. F. Trum, *Chairman*; W. D. Carlson; R. F. Cowing; R. D. Moseley, Jr.; W. H. Rhodes; J. H. Rust; G. B. Schnelle; and C. B. Braestrup, *Consultant*.

NCRP Report No. 37, issued on October 1, 1970, is titled Precautions in the Management of Patients who Have Received Therapeutic Amounts of Radionuclides.

This report is designed to serve as a guide for persons (including physicians, nurses, and funeral directors) concerned with the patient who has received a therapeutic dose of a radionuclide. It is a revision and enlargement of NCRP Report No. 21, Safe Handling of Bodies Containing Radioactive Isotopes (National Bureau of Standards

Handbook 65). With the increasing use of radionuclides in therapy, a more comprehensive consideration of the problem, including that of the ambulatory radioactive patient, is desirable. Four situations are of interest: (1) the patient receiving regular nursing care in the hospital; (2) the patient referred for emergency surgery; (3) the patient released from the hospital while still containing an appreciable quantity of the radionuclide; (4) the patient who dies while appreciably radioactive. The present report includes information and recommendations on all of these points for a larger number of radionuclides than were considered in the earlier NCRP report.

This report is directed primarily to problems encountered in the general hospital where the therapeutic use of radioactive material is occasional rather than carried out on an intensive scale. For the few large radiation centers more detailed and specialized provisions may be necessary, and can be developed from the principles given here.

Similar to Report No. 36, this report is also intended to serve as a guide to good practice. It provides basic standards which may be used in the preparation of regulatory protection codes, but is not specifically

written for literal adoption as legal regulations. Radiation sources discussed in this report may be subject to regulation by Federal, State or local governmental agencies. Such regulations may involve registration, licensing or compliance with specific rules.

The report also contains 6 appendices: I. Calculation of Accumulated Exposure; II. Typical Radioactivity Tags and Labels for Patient's Chart, Room, etc.; III. Radiation Safety Check List for Discharged Patients Containing Radionuclides; IV. Instructions for Family of Released Patient; V. An Acceptable Form for Radioactivity Report Accompanying Body; and VI. Method of Calculation of Beta Dose.

The report was prepared by the Council's Scientific Committee 13 on Safe Handling of Bodies Containing Radionuclides. Serving on the Committee during the preparation of this report were: E. H. Quimby, Chairman; S. Feitelberg (deceased); J. S. Laughlin; W. B. Stewart; R. Yalow; and E. G. Maier, Consultant.

For detailed information on these 2 Reports and the availability of other NCRP Reports, please write to W. Roger Ney, Executive Director, NCRP Publications, P.O. Box 4867, Washington, D.C. 20008.



# **NEWS ITEMS**

# RADIATION PROTECTION STANDARDS: QUO VADIS?

Health Physics Society Midyear Topical Symposium

The Sixth Annual Health Physics Society Midyear Topical Symposium titled "Radiation Protection Standards: Quo Vadis?" will be held at the Rivershore Motel in Richland, Washington, November 2–5, 1971.

The Symposium will seek to explore trends in radiation protection standards and critically examine existing standards and methodology. Specific topics include: 1. A Critical Examination of the Standards Setting Process. 2. Biological Basis for Radiation Protection Standards: Fact or Fiction? 3. Experiences in the Interpretation and Application of Radiation Protection Standards. 4. Derivation and Application of Radiological Design Standards to Plutonium Handling Facilities. 5. Standardization and Certification of Radiological Instrumentation and Dosimeters. 6. Surface Contamination Standards.

Abstracts of contributed papers must be received no later than June 1, 1971.

Further information, registration and abstract forms can be obtained from J. M. Selby, Symposium Chairman, Battelle-Northwest, P.O. Box 999, Richland, Washington 99352.

## TWENTY-THIRD ANNUAL JOSEPH AND SAMUEL FREEDMAN LECTURES IN DIAGNOSTIC RADIOLOGY

On Saturday and Sunday, April 17 and 18, 1971, Dr. William B. Seaman, Director of Radiology, The Presbyterian Hospital at Columbia-Presbyterian Medical Center, New York City, will deliver the Twenty-third Annual Joseph and Samuel Freedman Lectures in Diagnostic Radiology at the University of Cincinnati College of Medicine.

Physicians desiring to attend are requested to write Dr. Benjamin Felson, Department of Radiology, Cincinnati General Hospital, for further details.

## THIRTEENTH ANNUAL REFRESHER COURSE IN DIAGNOSTIC ROENTGENOLOGY

University of Cincinnati Medical Center

The Thirteenth Annual Refresher Course in Diagnostic Roentgenology will be held by the Radiology Department of the University of Cincinnati College of Medicine under the direction of Dr. Benjamin Felson from June 1 to 5, 1971.

The course will include, in addition to lectures and demonstrations, teaching methods employing audience participation. Saturday, June 5, will be devoted entirely to radiation physics.

Further information concerning the course, which is open to radiologists and radiology residents, may be obtained by writing to Dr. Harold B. Spitz, Department of Radiology, Cincinnati General Hospital, Cincinnati, Ohio 45229.

## MONTANA RADIOLOGICAL SOCIETY

The Montana Radiological Society's biennial Symposium will be held at the Holiday Inn, Bozeman, Montana, July 28–30, 1971.

Additional information may be obtained from Colvin H. Agnew, M.D., President, Box 1534, Billings, Montana 59102.

## INTERNATIONAL CONFERENCE ON LUMINESCENCE DOSIMETRY

The Third International Conference on Luminescence Dosimetry (TLD, RPL, TSEE, etc.) will be held in Riso near Copenhagen, Denmark, October 11–14, 1971.

For submission of abstracts and attendance information please write to Dr. Klaus Becker, Health Physics Division, Oak Ridge National Lab., Oak Ridge, Tennessee 37830.

# **BOOK REVIEWS**

MEDICAL NEUROLOGY. By John Gilroy, M.D., F.R.C.P. (Can.), Professor of Neurology, Wayne State University School of Medicine; Attending Neurologist, Detroit General and Harper Hospitals, Detroit, Mich.; and John Stirling Meyer, M.D., Professor and Chairman, Department of Neurology, Baylor College of Medicine; Chief, Department of Neurology, Methodist and Ben Taub Hospitals, Houston. Formerly; Professor and Chairman, Department of Neurology, Wayne State University School of Medicine, Detroit; Instructor in Neurology, Harvard Medical School, Boston, Mass. Cloth. Pp. 720, with some illustrations, The Macmillan Company, 866 Third Avenue, New York, N. Y. 10022, 1969.

The opinions expressed in this review are directed to radiologists; they represent the experience and resultant convictions of one whose primary interest is in neuroradiology.

The volume physically is well constituted from the standpoint of printing techniques and presentation of a massive amount of reference material. The index is adequate. The volume is more a reference work than it is a textbook, and probably would be consulted regularly if it were available in radiology departments, where an average amount of neuroradiology is undertaken. The value of the book to radiologists resides in the short and, for the most part, easily understood descriptions of common as well as rare neurologic diseases. Although this reviewer is in no sense a neurologist, it seems apparent that the descriptions of the physical and historical distinctions among these diseases will serve as an interesting background for the neuroradiologic features which must be studied elsewhere.

It is quite understandable that in a reference book of this size it would be impossible to discuss the neuroradiologic features in any great detail. However, the authors do not attach any significant value to the possibility of consulting with radiologists in the investigation of the many clinical entities in which such a collaboration would be of benefit to both disciplines.

Probably the most interesting part of the book, from a radiologic point of view, is Chapter 9, on cerebral vascular disease. The attrac-

tiveness of this chapter arises from the organization of important aspects of neurovascular disease, together with valuable descriptions of these clinical entities which form an increasingly large segment of neuroradiologic practice, although the chapter itself is not very informative so far as roentgenologic technique and interpretation are concerned. It seems obvious that neurovascular diseases are only now becoming of great interest to classical neurologists, an impression which is strengthened by the curious discrepancy between the details of neuroanatomy which are presumed to be known by the reader and the parallel presumption that the same reader knows virtually nothing about special features of the vascular anatomy of the brain and spinal cord. The author's rather indifferent interest in neuroradiology is decisively exposed by a sentence on page 586: "Arteriography is frequently unrewarding in posterior fossa tumors with the exception of vascular malformations, large vascular tumors such as meningiomas, or tumors and cysts causing marked displacement of the branches of the basilar artery." A cursory examination of neuroradiologic literature published particularly within the last few years should convince nearly anyone that there has indeed been an enormous amount of work undertaken in just this field, and that there is a great deal of information to be gained from such arteriography when it is properly performed.

In conclusion, it can be said that this volume may be a helpful reference book for radiologists as well as neurologists; however, probably not for the same reasons. It is well known that the authors are eminent in their field and that they have had access to a large volume of clinical data. There is no doubt that the book would be a worthwhlie addition to a departmental library. However, the personal opinion of the reviewer is that the volume would have been more valuable had the allusions to radiology been omitted entirely from the text, and if, instead, outstanding references to the radiologic features had been included in the otherwise eminently useful reference lists appended to each chapter. Surely, any modern volume on medical neurology should emphasize the benefits to the patient of close and critical collaboration between the clinical neurologist and the experienced specialists who know how to plan, perform, and interpret the general and special roentgenographic studies which are now so much a part of the diagnosis and management of many neurologic disorders.

COLIN B. HOLMAN, M.D.

TRAITÉ DE RADIODIAGNOSTIC. Volume VIII. Appareils Urinaire et Génital Masculin; Surrénales. By Guy Lemaitre, Radiologiste des Hôpitaux de Lille; Jean-René Michel, Radiologiste des Hôpitaux de Paris; and Jean Tavernier, Radiologiste des Hôpitaux de Bordeaux; with J. Rémy, Ch. Sulman, J. Swyngedauw, and B. Vasselle. Cloth. Pp. 580, with 645 figures. Price, 270 F. Masson & Cie, Éditeurs, 120, Boulevard Saint-Germain, Paris, 1970.

Volume VIII comes as the third volume of a planned series of XX devoted to Radiodiagnosis. The two volumes previously issued are "The Radiological Image" (Volume I) and "Bone, General Pathology" (Volume X).

Volume VIII is divided into 4 major sections: Part I—The Kidney and Ureter; Part II—The Lower Urinary Tract and Male Genital Apparatus; Part III—Radio-Isotopic Renal Exploration; and Part IV—Adrenals.

The general presentation is very attractive. The particular typography used makes reading pleasant. The divisions and subdivisions of each chapter are clearly indicated. A short and elective bibliography completes each chapter. A practical alphabetical index permits quick reference to any subject under discussion.

As in many European publications, the roentgenograms are reproduced in negative. These reproductions are well defined and demonstrative. Schematic drawings, when required, provide clarification in more complicated cases.

All the valuable contributions accumulated over the years are briefly presented, accompanied by pertinent physiopathologic explanations. Also included are the more recently described syndromes such as medullary sponge kidney, peripelvic cyst, "the kidney as a part of the organism" (in mulitple myeloma, atherosclerosis, retroperitoneal tumors, parasitoses), and renal malformations in phakomatoses.

Lithiasis is discussed under local renal lithiasis, as opposed to systemic lithiasis (encountered in hyperparathyroidism, osteolytic processes, metabolic or iatrogenic origin, etc.).

The most recent radiologic operative techniques are also presented: renal angiography, selective catheterization of renal and adrenal arteries, and functional scannography. All these examinations have contributed to improved analysis of the urographic image.

This textbook is highly recommended to all those specializing or interested in the field of uroradiology.

H.P. Lévesque, M.D.

## BOOKS RECEIVED

PATHOLOGY OF IRRADIATION. Edited by Charles C. Berdjis, M.D., Colonel, Medical Corps, U. S. Army; Armed Forces Institute of Pathology, Washington, D. C. Cloth. Pp. 710, with some illustrations. Price, \$49.50. Williams & Wilkins Company, 428 E. Preston Street, Baltimore, Md. 21202, 1971.

CARE OF THE PATIENT IN DIAGNOSTIC RADIOGRAPHY. Third edition. By D. Noreen Chesney, Hon.F.S.R., T.E., Superintendent Teacher, School of Radiography, Coventry and Warwickshire Hospital; and Muriel O. Chesney, F.S.R., T.E., Teacher-Principal, School of Radiography, The United Birmingham Hospital, England. Cloth. Pp. 304, with 49 illustrations. Price, \$8.00. F. A. Davis Company, 1915 Arch Street, Philadelphia, Pa. 19103, 1970.

Annual Review of Nuclear Science. Volume 20. Editor, Emilio Segrè, University of California, Berkeley; Associate Editor, J. Robb Grover, Brookhaven National Laboratory; Associate Editor, H. Pierre Noyes, Stanford University. Cloth. Pp. 613, with some figures. Price, \$10.00. Annual Review Inc., 4139 El Camino Way, Palo Alto, Calif. 94306, 1970.

MEDICAL RADIATION PHYSICS. By William R. Hendee, Ph.D., Associate Professor of Radiology, University of Colorado Medical Center, Denver, Col. Cloth. Pp. 599, with many figures. Price, \$25.00. Year Book Publishers, 35 East Wacker Drive, Chicago, Ill. 60601, 1970.

EYE INJUNIES. By Edward Zagora, M.D., Lecturer of Ophthalmology, University of Sherbrooke, Canada. Cloth. Pp. 601, with many illustrations. Price. \$30.75. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill. 62703, 1970.

THE HISTOGENESIS OF THYROID CANCER. By N. Simionescu, Institute of Endocrinology, Department of Morphology, Bucharest, Romania. Cloth. Pp. 173, with many illustrations. Price, \$22.75. Grune & Stratton, 757 Third Avenue, New York, N. Y. 10017, 1970.

PROTECTION AGAINST IONIZING RADIATION FROM EX-TERNAL SOURCES. A Report by Committee 3 of the International Commission on Radiological Protection. ICRP Publication No. 15. Paper. Pp. 34-Price, \$3.75. Published for ICRP by Pergamon Press, Maxwell House, Fairview Park, Elmsford,

N. Y. 10523, 1970.

ARTÉRIOGRAPHIE DE LA CAROTIDE EXTERNE: ÉTUDE ANATOMO-RADIOLOGIQUE ET CLINIQUE. By C. Aaron, D. Doyon, H. Fischgold, J. Metzger, and J. Richard. Paper. Pp. 118, with 135 figures. Price. 66 F. Masson & Cie, 120 Boulevard Saint-Germain,

Paris, France, 1970.

Acoustic Nerve Tumors: Early Diagnosis and TREATMENT. Second edition. By J. Lawrence Pool, M.D., D. Med. Sci., Professor of Neurological Surgery, Columbia University: Chairman of Service of Neurological Surgery, The Neurological Institute of New York Presbyterian Hospital, New York; Arthur A. Pava, M.D., Chief of Neurological Surgery, Wesson Memorial Hospital, Springfield, Mass.; and Elliott C. Greenfield, M.D., Staff Surgeon, Otolaryngology, Long Island Jewish Medical Center, New Hyde Park, N. Y.; formerly: Assistant Professor of Otolaryngology, Columbia University College of Physicians and Surgeons; Assistant Attending Otolaryngologist, Presbyterian Hospital, New York, N. Y. Cloth. Pp. 232, with many figures. Price \$13.50. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill. 62703, 1970.

CANCER; DIAGNOSIS, TREATMENT, AND PROGNOSIS. Fourth edition. By Lauren V. Ackerman, M.D., Professor of Surgical Pathology and Pathology, Washington University School of Medicine, St. Louis, Mo.; Surgical Pathologist-in-Chief to Barnes and Affiliated Hospitals and St. Louis Children's Hospital, St. Louis, Mo.; Consultant, Ellis Fischel State Cancer Hospital, Columbia, Mo.; Consultant, Armed Forces Institute of Pathology; Visiting Professor of Surgical Pathology, University of Witwatersrand, Johannesburg, R.S.A. (1969); and Juan A. del Regato, M.D., Di-

rector, Penrose Cancer Hospital, Colorado Springs, Colo; Clinical Professor of Radiology, University of Colorado School of Medicine; Member, National Advisory Cancer Council; Member, Board of Chancellors, American College of Radiology; Member, Advisory Commission on Biology and Medicine, Puerto Rico Nuclear Center; Member, Committee on the Genito-Urinary System, National Academy of Science-National Research Council. Cloth. Pp. 1,049, with 783 figures. Price, \$39.50. C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. 63103, 1970.

JOINT FAO/WHO EXPERT COMMITTEE ON MILK HYGIENE. Third Report, Geneva, April 22–28, 1969. Paper. Pp. 82. Price, \$1.25. World Health Organization, Geneva, 1970. The American Public Health Association, Inc., 1740 Broadway, New

York, N. Y. 10019, 1970.

PROTECTION OF THE PATIENT IN X-RAY DIAGNOSIS.

A Report prepared by a task group of Committee 3 of the International Commission on Radiological Protection. ICRP Publication No. 16. Paper. Pp. 46. Price, \$4.75. Published for ICRP by Pergamon Press, Maxwell House, Fairview Park, Elmsford, N. Y. 10523, 1970.

THE ENVIRONMENTAL RADIATION SURVEILLANCE LABORATORY: A GUIDE TO DESIGN, LAYOUT, STAFF AND EQUIPMENT REQUIREMENTS. By P. R. Kamath, Health Physics Division, Bhabha Atomic Research Centre, Trombay, Bombay, India. Paper. Pp. 44. Price, \$2.00. World Health Organization, Geneva, 1970. The American Public Health Association, Inc., 1740 Broadway, New York, N. Y. 10019, 1970.

ERGEBNISSE DER MEDIZINISCHEN RADIOLOGIE. By Rolf Glauner, Alois Rüttimann, Peter Thurn, Manuel Viamonte, and Erich Vogler. Paper. Pp. 160, with many illustrations. Price, DM 79.-. Georg Thieme Verlag. In U.S.A. and Canada, Intercontinental Medical Book Corporation, New York, N. Y. 10016, 1970.



# SOCIETY PROCEEDINGS

# MEETINGS OF RADIOLOGICAL SOCIETIES\*

### United States of America

AMERICAN ROBNTOEN RAY SOCIETY

Secretary, Dr. Ted F. Leigh, Emory University Clinic, Atlanta, Ga. 30322. Annual meeting: Sheraton Hotel, Boston, Mass., September 28-October 1, 1971.

AMERICAN RADIUM SOCIETY

Secretary, Dr. Jerome M. Vaeth, Saroni Tumor Institute, 1600 Divisadero St., San Francisco, Calif. 94115. Annual meeting: Mexico City, Mexico, March 15-18, 1971.

RADIOLOGICAL SOCIETY OF NORTH AMERICA Secretary-Treasurer, Dr. Maurice Doyle Frazer, 1744 South Fifty-eighth St., Lincoln, Neb. Annual meeting: Palmer House, Chicago, Ill., November 28-December 3,

1971.

AMERICAN COLLEGE OF RADIOLOGY

Executive Director, William C. Stronach, 20 N. Wacker

Drive, Chicago 6, Ill. Annual meeting: St. Louis, Mo.,

Chase-Park Hotel, March 30-April 3, 1971.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION

Secretary, Dr. Ted F. Leigh, Emory University Clinic,

Atlanta, Ga., 30322. Annual meeting: Atlantic City,

N. I. June 20-24, 1071.

N. J., June 20-24, 1971.

AMERICAN BOARD OF RADIOLOGY

Secretary, Dr. C. Allen Good. Correspondence should be directed to Kahler East, Rochester, Minn. 55901.

Oral examinations will be held in the following cities

oral examinations will be need in the following cities during the next 2 years: Bal Harbour, Fla., June 7-11, 1971, Americana Hotel; Dallas, Tex., Dec. 6-10, 1971, Statler-Hilton Hotel; Washington, D.C., June 5-9, 1972, Washington-Hilton Hotel; and Atlanta, Ga., Dec. 4-8, 1972, Sheraton-Biltmore Hotel.

Written examinations are scheduled in June of each

year in 13 large centers, and applications must be received in the Board Office before Sept. 30 of the year preceding the one in which the candidate wishes to be examined. The written examinations this year will be

held on June 19, 1971.

Deadline for filing applications for any examination

in 1972 is September 30, 1971.

American Association of Physicists in Medicine Secretary, Leonard Stanton, Hahnemann Medical College, 230 N. Broad St., Philadelphia, Pa. 19102. Annual meeting to be announced.

AMERICAN SOCIETY OF THERAPBUTIC RADIOLOGISTS Secretary, Dr. Carl R. Bogardus, Jr., University of Okla-homa Medical Center, Oklahoma City, Oklahoma 73104

AMERICAN INSTITUTE OF ULTRASOUND IN MEDICINE Secretary, F. J. Fry, M.Sc., Bioacoustics Lab., University of Illinois, Urbana, Ill.

American Society of Neuroradiology Secretary-Treasurer, Dr. Eugene V. Leslie, Edward J. Meyer Memorial Hospital, 462 Grider St., Buffalo, N. Y.

THIRTEENTH INTERNATIONAL CONGRESS OF RADIOLOGY Meeting: Madrid, Spain, Oct. 13-19, 1973.

TENTH INTER-AMERICAN CONGRESS OF RADIOLOGY Counselor for the United States, Dr. Manuel Viamonte, Jr., University of Miami School of Medicine, Jackson Memorial Hospital, Miami Fla. 33136.

President, Dr. Victor A. Marcial, Puerto Rico Nuclear Center, Caparra Heights Station, San Juan, Puerto Rico 00935.

Meeting: San Jeronimo-Hilton Hotel, San Juan, Puerto Rico, May 16-22, 1971.

Inter-American College of Radiology President, Dr. Juan A. del Regato, Penrose Cancer Hospital, 2215 North Cascade Ave., Colorado Springs, Colo. 80907.

Second Congress of the European Association of RADIOLOGY

President, Professor Dr. J. R. von Ronnen, State Uni-

Versity of Leiden, The Netherlands.

Secretariat, c/o Holland Organizing Centre, 16 Lange Voorhout, The Hague, The Netherlands. Congress Meeting: Amsterdam, The Netherlands, June 14-18,

FIRST ASIAN AND OCEANIAN CONGRESS OF RADIOLOGY
Honorary Secretary, Dr. J. J. Martin, Box 805 F., G.P.O., Melbourne, 3001, Australia. Meeting: Melbourne, Australia, Nov. 22-26, 1971

ALABAMA CHAPTER OF ACR Secretary, Dr. William V. Weldon, Medical Arts Building, Birmingham, Ala. 35205. Meets time and place of Alabama State Medical Association.

Alaska Radiological Society

Secretary, Dr. Bruce C. Wright, Providence Hospital, Anchorage, Alaska. Meets third Wednesday each month. ARIZONA RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary, Dr. Wesley S. Fee, 2421 E. 6th St., Tucson, Ariz. 85719. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

ARKANSAS CHAPTER OF ACR Secretary-Treasurer, Dr. Wilma C. Diner, Univ. of Arkansas Medical Center, Little Rock, Ark. 72201. Meets twice annually, the Spring Meeting being in conjunction with and at the place of the State Medical Association.

Association of University Radiologists Secretary-Treasurer, Dr. Elliott C. Lasser, University Hospital of San Diego County, San Diego, Calif. 92103. Annual Meeting: Durham, N. C., May 13–15, 1971, with the Duke University and University of North Carolina

Radiology Departments serving, as co-hosts. ATLANTA RADIOLOGICAL SOCIETY Secretary, Dr. Richard S. Colvin, Emory University Clinic, Atlanta, Ga. 30322. Meets on four Thursday evenings during the academic year at a time announced in early September of each year, at the Academy of Medicine, Atlanta, Ga., at 8:00 P.M.

BAVARIAN-AMERICAN RADIOLOGIC SOCIETY

Advisor, Colonel Paul E. Sieber. Secretary, LTC Peter
B. Riesz, USAH Bad Cannstatt, APO 09154, New York,

N. Y. Meets quarterly.
BLOCKLEY RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. R. John Gould, 41 Lombardy

Rd., Drexel Hill, Pa. 19026. BLUEGRASS RADIOLOGICAL SOCIETY

Secretary-Treasurer, Joseph A. Sayeg, Ph.D., Radiation Physicist, University of Kentucky, Lexington, Ky. 40506. The Society meets once each month during the school year.

BROWN RADIOLOGICAL SOCIETY, NEW YORK STATE, CHAP-TER ACR

Secretary-Treasurer, Dr. David Bruce Hayt, 600 E. 233rd St., Bronx, N. Y. 10466. Meets 4 times a year.

Brooklyn Radiological Society Secretary-Treasurer, Dr. Kenneth B. Robinson, 301 E 75th St., Apt. 11-A, New York, N.Y. 10021. Meets first Thursday of each month, October through June.

BUFFALO RADIOLOGICAL SOCIETY Secretary, Dr. Glen M. Ebersole, 405 Spring St., Jamestown, N.Y. 14701. Meets second Monday evening each month, October to May inclusive, at University Club.

<sup>\*</sup> Secretaries of societies are requested to send timely information promptly to the Editor.

CALIFORNIA RADIOLOGICAL SOCIETY, CALIFORNIA CHAPTER

Secretary-Treasurer, Dr. John L. Gwinn, Childrens Hospital of Los Angeles, P.O. Box 54700, Los Angeles, Calif.

CATAWBA VALLEY RADIOLOGICAL SOCIETY

Secretary, Dr. Emmett R. White, P. O. Box 10, Rutherford College, N. C. 28671. Meets every Thursday, Dept. of Radiology, Valdese General Hosp., Valdese, N. C., at

CENTRAL NEW YORK RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. David N. Cheris, Community General Hospital of Greater Syracuse, Broad Road, Syracuse, N. Y. 13215. Meets first Monday each month October through May.

CENTRAL OHIO RADIOLOGICAL SOCIETY

Secretary, Dr. James V. Blazek, 2586 Lane Rd., Columbus, Ohio 43220. Meets second Thursday in October, November, January, and March 15, and May 19 at Fort Hayes Hotel, Columbus, Ohio.

CHICAGO ROBNTGEN SOCIETY

Secretary-Treasurer, Dr. William T. Moss, 250 E. Superior St., Chicago, Ill. 60611. Meets third Thursday of each month, October to April, except December, at the

Bismarck Hotel, Chicago, Ill. CLEVELAND RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Daniel E. Wertman, 11311 Shaker Blvd., Cleveland, Ohio 44104. Meetings at 7:00 P.M. on fourth Monday of October, November, January,

February, March and April.
Colorado Radiological Society, Chapter of ACR Secretary, Dr. Marvin L. Daves, Univ. of Colorado Medical Center, 4200 E. Ninth Ave., Denver, Colo. 80220. Meets third Friday of each month at Denver

Athletic Club from September through May.

Connecticut Valley Radiologic Society

Secretary, Dr. William W. Walthall, Jr., 130 Maple St.,

Springfield, Mass. Meets in April and October.

DALLAS-FORT WORTH RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Fred H. Dunn, 5940 Forest Park Rd., Suite 101, Dallas, Tex. 75235. Meets the 3rd Monday of every month at 6:30 P.M., at the Cibola Inn, Arlington, Tex.

DELAWARE CHAPTER OF ACR

Secretary, Dr. James H. Taylor, Wilmington Medical Center, Wilmington, Del. 19899.

EAST BAY RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. S. Walter Kran, Doctors' Hospital of San Leandro, 1385 East 14th St., San Leandro, Calif. 94578. Meets first Thursday each month, Oct. through May, at University Club, Oakland, Calif.

EAST TENNESSEE RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Eberhard F. Besemann, Baroness Erlanger Hospital, Chattanooga, Tenn. 37403. Meets in January and September.

FLORIDA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Wm. F. Lindsey, 1215 Hodges Dr., Tallahassee, Fla. 32303. Meets twice annually, in the spring with the annual State Society Meeting and in the fall.

FLORIDA WEST COAST RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Allen L. Sheer, University Community Hospital, 13505 N. 31st St., Tampa, Fla. 33612. Meets in January, March, May, July, September and November.

GEORGIA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. Walker Harris, The Medical Center,
Columbus, Ga. 31902. Meets in spring and fall at Annual State Society Meeting.
GREATER CINCINNATI RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Owen L. Brown, 2421 Auburn Ave., Cincinnati, Ohio 45219.

GREATER LOUISVILLE RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. L. D. LeNeave, 315 E. Broadway, Louisville, Ky. 40202. Meets monthly.

GREATER MIAMI RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. John Kathe, North Shore Hospital, Miami, Fla. 33150. Meets monthly, third Wednes-

day at 8 200 P.M. at various member hospitals, Miami, Fla. GREATER ST. LOUIS SOCIETY OF RADIOLOGISTS Secretary-Treasurer, Dr. Roland P. Ernst, 3720 Wash-

ington Ave., St. Louis, Mo. 63108.

HAWAH RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary-Treasurer, Dr. Virgil R. Jobe, Jr., 888 South

King St., Honolulu, Hawaii 96813. Meets third Monday of each month at 7:30 P.M.

HEALTH PHYSICS SOCIETY Secretary. John H. Pingel, Argonne National Laboratory, 9700 S. Cass Ave., Argonne, Ill. 60439. Annual Meeting: Waldorf Astoria Hotel, New York City, July 11-15,

HOUSTON RADIOLOGICAL SOCIETY Secretary, Dr. Kenneth M. Jensen, 1615 St. Joseph Prof. Bldg., Houston, Texas 77002. Meets fourth Monday of each month, except June, July, August and December, at 6:00 P.M., at 103 Jesse H. Jones Library Building, Texas Medical Center, Houston, Tex. 77025
IDAHO STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Hugh P. Smith, Jr., 130 E. Bannock, Boise, Id. 83702. Meets in the spring and fall. ILLINOIS RADIOLOGICAL SOCIETY, INC., CHAPTER OF ACR Secretary, Dr. Jack L. Melamed, 1230 Sunset Rd. Winnetka, Ill. 60093. Meets in the spring and fall. INDIANA ROENTOEN SOCIETY, INC., CHAPTER OF ACR Secretary, Dr. Dale B. Parshall, Elkhart General Hospital, P.O. Box 1329, Elkhart, Ind. 46514.
IOWA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. John Huston Jr., 1948 First Bldg., Houston, Texas 77002. Meets fourth Monday of

Secretary-Treasurer, Dr. John Huston Jr., 1948 First Ave. N.E., Cedar Rapids, Iowa 52402. Luncheon and

business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

KANSAS RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Wm. R. Allen, 155 S. 18th St. Kansas City, Kan. 66102. Meets in spring with State Medical Society and in winter on call.

KENTUCKY CHAPTER OF ACR
Secretary-Treasurer, Dr. Joan R. Hale, 402 Heyburn
Bldg. Louisville, Ky. 40202. Meets in April and September.

Kings County Radiological Society

Secretary, Dr. Sidney Hendler, 1880 Ocean Ave., Brooklyn 30, N.Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

KNOXVILLE RADIOLOGICAL SOCIETY
Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

LONG ISLAND RADIOLOGICAL SOCIETY

Secretary, Dr. Harold L. Atkins, 1200 Stewart Ave., Garden City, N. Y. 11533. Meets monthly.

Los Angeles Radiological Society

Secretary, Dr. Harry T. Vanley, St. Mary's Long Beach Hospital, Long Beach, Calif. 90083. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles, Calif.

LOUISIANA-TEXAS GULF COAST RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Edward A. Sheldon, 109 Doctors

Bldg., Beaumont, Tex. 77701

MAINE RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Richard W. Taylor, Radiology Department, St. Mary's General Hospital, Lewiston, Maine 04240. Meets in June, September, December and April.

MARYLAND RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Nathan Stofberg, 4519 Hawksbury Rd., Pikesville, Md. 21208.

MASSACHUSETTS RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Norman L. Siadowsky, The Faulkner Hosp., 1153 Centre St., Jamaica Plain, Mass. 02130 MEMPHIS ROENTORN SOCIET

Secretary-Treasurer, Dr. Webster Riggs, Jr., The University of Tennessee College of Medicine, Department of Radiology, Walter F. Chandler Bldg., 865 Jefferson Ave., Memphis, Tenn. 38103. Meets first Monday of each month at John Gaston Hospital.

MIAMI VALLEY RADIOLOGICAL SOCIETY Secretary, Dr. Darwood B. Hance, Reid Memorial Hospital, Richmond, Ind. Meets third Thursday of fall, winter and spring months at 7:30 P.M. at Miami Valley Hospital, Dayton, Ohio.
Michigan Radiological Society, Chapter of ACR

Secretary, Dr. David P. Corbett, Harper Hospital, Detroit, Mich. 48201. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antie-

tam, at 6:30 P.M.

MID-HUDSON RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Herbert S. Berlin, Hopewell Junction, N. Y. Meets 7:00 P.M., first Wednesday of each month, September to May.

MILWAUKEE ROENTGEN RAY SOCIETY

Secretary-Treasurer, Dr. James E. Bell, 8700 W. Wisconsin Ave., Milwaukee, Wis. 53213. Meets monthly on fourth Monday, October through May, at University Club.

MINNESOTA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Warren L. Kump, 4243 Glenwood Ave., Minneapolis, Minn. 55422. Meets twice annually, fall and winter.

MISSISSIPPI STATE RADIOLOGICAL SOCIETY, CHAPTER OF

Secretary-Treasurer, Dr. Ottis G. Ball, 5356 Balmoral Drive, Jackson, Miss. 39211. Meets third Thursday of each month at the Heidelberg Hotel, Jackson, at 6:00 P.M.

MISSOURI RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Arthur A. Porporis, 100 N. Euclid Ave., St. Louis, Mo. 63108.

MONTANA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Jon A. Anderson, Doctor's Building, 1231 N. 29th Street, Billings, Mont. 59101.

NEBRASKA CHAPTER OF ACR

Secretary-Treasurer, Dr. Gordon F. Johnson, 4239 Farnam, Omaha, Neb. 68131. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

NEVADA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Harris W. Knudson, 2020 W. Charleston

Blvd., Las Vegas, Nev. 89102. New England Roentoen Ray Society

Secretary, Dr. Stefan C. Schatzki, 1180 Beacon St., Brookline Mass. 02146. Meets third Friday of each month, October through April, excluding December, at The Longwood Towers, 20 Chapel Street, Brookline, Mass.,

at 4:30 p.m. New Hampshire Roentoen Ray Society, Chapter or

Secretary, George Farmlett, 33 Round Bay Rd., Keene, N. H. 03246. Meets four to six times yearly.

New Mexico Society of Radiologists Chapter of ACR Secretary, Dr. Donald A. Wolfel, Albuquerque, New Mexico. Four meetings annually, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

NEW YORK ROENTGEN SOCIETY Secretary-Treasurer, Dr. Samuel H. Madell, 1. E. 82nd St., New York, N. Y. 10028. Meets monthly on third Monday at the New York Academy of Medicine at 4:30 P.M. Annual Spring Conference: Waldorf Astoria Hotel, New York, April 29-May 1, 1971. Further information may be obtained from Dr. Albert A. Dunn, Roosevelt Hosp.,

New York, N. Y. 10019. New York State Chapter of ACR

Secretary-Treasurer, Dr. John J. Magovern, 520 Frank-lin Ave., Garden City, N. Y. 11530. North Carolina Chapter of ACR.

Secretary-Treasurer, Dr. James F. Martin, 300 S. Haw-

thorne Road, Winston-Salem, N. C. 27103.

NORTH DAKOTA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Marshall Landa, 1702 13th St., So., Fargo, N. D. 58102. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

NORTH FLORIDA RADIOLOGICAL SOCIETY

Secretary, Dr. John W. Morris, III., Department of Radiology, Halifax District Hospital, Daytona Beach, Fla. 32015. Meets quarterly in March, June, September and December.

NORTHEASTERN NEW YORK RADIOLOGICAL SOCIETY Secretary, Dr. Barbara Chick, Glens Falls Hospital, Glens Falls, N.Y. 12801. Meets in Albany area on third Wednesday of October, November, March, April, and May.

NORTHERN CALIFORNIA RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Kevin Ryan, Woodland Medical group, Woodland, Calif. 95695. Meets fourth Monday of Sept., Nov., Jan., March and May at Aldo's Restaurant in Sacramento.

Northwestern Ohio Radiological Society
Secretary, Dr. Vito J. Zupa, Mercy Hospital, Department
of Radiology, Toledo, Ohio.
Ohio State Radiological Society, Chapter of ACR

Secretary, Dr. Joseph Hanson, 1544 South Byrne Road, Toledo, Ohio 43614.

OKLAHOMA STATE RADIOLOGICAL SOCIETY, CHAPTER OF

Secretary, Dr. Richard B. Price, 204 Medical Tower Bldg., Oklahoma City, Okla. 73112. Meets in January, May and October.

ORANGE COUNTY RADIOLOGICAL SOCIETY Secretary, Dr. Edward I. Miller, 301 Newport Blvd., Newport Beach, Calif. 92660. Meets on fourth Tuesday of the month, excluding June, July, August, and December, at the Orange County Medical Association Bldg., Orange, Calif.

OREGON STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Gerlad L. Warnock, 11699 N. E. Glisan St., Portland, Ore. 97220. Meets on second Wednesday of month, October through April, at the University Club, Portland, Ore.

ORLEANS PARISH RADIOLOGICAL SOCIETY Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans, La. 70113. Meets second Tuesday of each month.

PACIFIC NORTHWEST RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Robert S. Miller, 13753 S.W. Farmington Rd.; Beaverton, Oregon 97005. Meets annually in Portland, Oregon, Seattle, Washington or Victoria or Vancouver, British Columbia, in early May.

PENNSYLVANIA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Theodore A. Tristan, Harrisburg Polyclinic Hosp., Harrisburg, Pa. 17105.
PHILADELPHIA ROBNTOEN RAY SOCIETY

Secretary, Dr. C. Jules Rominger, Misericordia Hospital, 54th St. and Cedar Ave., Philadelphia, Pa. 19143. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

PITTSBURGH ROENTGEN SOCIETY Secretary, Dr. Stephen C. Bruno, Shadyside Hospital, 5230 Centre Ave., Pittsburgh, Pa. 15232. Meets second Wednesday of month, October through June, at Park Schenley Restaurant.

RADIATION RESEARCH SOCIETY

Executive Secretary, Richard J. Burk, Jr., 4211 39th St., N.W., Washington, D. C. 20016. Annual Meeting: Boston, Mass., May 9-13, 1971.

RADIOLOGICAL SOCIETY OF CONNECTICUT, INC., CHAPTER or ACR

Secretary-Treasurer, Dr. Carl W. Scheer, 335 Cook Ave., Meriden, Conn. 06450. Meetings are held quarterly RADIOLOGICAL SOCIETY OF GREATER CINCINNATI Secretary-Treasurer, Dr. Donald E. Gunderson, 3553

Bayard Dr., Cincinnati, Ohio 45208. Meets first Monday of each month at Cincinnati Academy of Medicine.

RADIOLOGICAL SOCIETY OF GREATER KANSAS CITY Secretary, Dr. Ken C. Davidson, St. Luke's Hospital of Kansas City, Kansas City, Mo. 84111. Meets 5 times a year on given dates.

RADIOLOGICAL SOCIETY OF KANSAS CITY

Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

RADIOLOGICAL SOCIETY OF LOUISIANA, CHAPTER OF ACR Secretary, Dr. Ralph B. Bergerson, 154 Brockenbraugh Ct. Metairie, La. 70005. Meets semiannually during Louisiana State Medical Society meeting and 6 months

RADIOLOGICAL SOCIETY OF NEW JERSEY, CHAPTER OF ACR Secretary, Dr. Sidney Ketyer, St. Elizabeth Hosp., 225 Williamson St., Elizabeth, N. J. 07207. Meets in Atlantic City at time of State Medical Society meeting and in October or November in Newark, N. J.

RADIOLOGICAL SOCIETY OF RHODE ISLAND, CHAPTER OF

Secretary-Treasurer, Dr. John J. O'Brien, 292 Merry-mount Dr., Warwick, R.I. 02888.

RADIOLOGICAL SOCIETY OF SOUTHERN CALIFORNIA Secretary-Treasurer, Dr. Gladden V. Elliott, 5565 Grossmont Center Dr., Suite 1, La Mesa, Calif. 92041. Meets three times a year, usually October, February and May. RADIOLOGICAL SOCIETY OF THE STATE OF NEW YORK

Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester, N. Y. 14618.

REDWOOD EMPIRE RADIOLOGICAL SOCIETY

Secretary, Dr. Lee F. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

RICHMOND COUNTY RADIOLOGICAL SOCIETY Secretary, Dr. M. Pinson Neal, Jr., Medical College of Virginia, 1200 E. Broad St., Richmond, Va. 23219. Meets first Thursday of each month at various hospitals.

ROCHESTER ROENTGEN RAY SOCIETY, ROCHESTER, N. Y. Secretary, Dr. Kenneth E. Robinson, Rochester General Hospital, 1425 Portland Ave., Rochester, N. Y. 14621. Quarterly meetings on the call of the President, at the Rochester Academy of Medicine.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Lorenz R. Wurtzebach, 4200 E. Ninth Ave., Denver. Colo. 80220. Annual meeting: Brown Palace Hotel, Denver, Colo., Aug. 19–21, 1971.

SAN ANTONIO-CIVILIAN-MILITARY RADIOLOGICAL SOCIETY Secretary, Dr. Lee F. Rogers, Department of Radiotherapy, Bexar County Teaching Hospital, 4502 Medical Drive, San Antonio, Texas. Meets third, Wednesday of each month at Fort Sam Houston Officers' Club at 6:30

SAN DIEGO RADIOLOGICAL SOCIETY

President-Secretary, Dr. James M. Lee, Scripps Clinic and Research Found., 476 Prospect St., La Jolla, Calif. 92037. Meets first Wednesday of each month at the Town & Country Hotel.

SAN FRANCISCO RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Warren M. Russel, Franklin
Hospital, Castro & Duboce, San Francisco, Calif. 94114.

Meets quarterly at various hospitals (contact Secretary).

SANTA CLARA COUNTY RADIOLOGICAL SOCIETY

Secretary, Dr. Emory G. West, 285 S. Drive, Mt. View, Calif. 94040. Meets monthly at the Santa Clara County Medical Association Bldg., 700 Empey Way, San Jose,

SECTION ON RADIOLOGY, CALIFORNIA MEDICAL ASSOCIATION Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Medical Society of the Dis-trict of Columbia

Secretary-Treasurer, Dr. Louis Wener, Cafritz Memorial Hosp., 1310 Southern Ave., S.E., Washington, D. C. 20032. Meets at Medical Society Library, third Wednes-

20032. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 p.m. SECTION ON RADIOLOGY, SOUTHERN MEDICAL ASSOCIATION Secretary, Dr. Phillip W. Voltz, Jr., 120 Medical Professional Bldg., San Antonio, Tex. 78212.

SECTION ON RADIOLOGY, TEXAS MEDICAL ASSOCIATION Secretary, Dr. George F. Crawford, St. Elizabeth Hospital, Beaumont, Tex. Meets annually with the Texas Medical Association Medical Association.

SHREVEPORT RADIOLOGICAL CLUB Secretary, Dr. W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday at 7:30 P.M., September to May inclusive.

SOCIETY FOR PEDIATRIC RADIOLOGY

Secretary, Dr. John L. Gwinn, Children's Hospital, 4614 Sunset Blvd., Los Angeles 27, Calif. Annual meeting: Sheraton Hotel, Boston, Mass., September 26–27, 1971.

SOCIETY OF NUCLEAR MEDICINE Secretary, Dr. James J. Smith, 140 E. 54th St., New York, N. Y. Administrative Officer, Mrs. Margaret Glos, 211 E. 43rd St., New York, N. Y. 10017. Annual meeting: Los Angeles, Calif., June 26-July 2, 1971.
SOUTH BAY RADIOLOGICAL SOCIETY

Months

Secretary, Dr. Emerson C. Curtis, University Dr., Menlo Park, Calif. 94025. Meets second Wednesday of each month.

SOUTH CAROLINA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

South Dakota Radiological Society, Chapter of ACR Secretary, Dr. Harkon O. Haugan, 716 Quincy St., Rapid City, S. D. 57701. Meets in spring with State Medical Society and in fall.

SOUTHERN CALIFORNIA RADIATION THERAPY SOCIETY Secretary-Treasurer, Dr. Aaron G. Fingerhut, 1000 W. Carson St., Torrance, Calif. 90502. Meets quarterly.

Southern Radiological Conference Secretary-Treasurer, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 7544, Mobile, Ala. 36607. Annual

meeting SOUTHWESTERN RADIOLOGICAL SOCIETY

Secretary, John M. McGuire, 904 Chelsea, El Paso, Tex. Meets last Monday of each month at 6:30 P.M. in

the Paso del Norte Hotel.

TENNESSEE RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Lawrence R. Nickell, Maury County Hospital, Columbia, Tenn. 38401. Meets annually at the time and place of the Tennessee State Medical Association meeting.

TEXAS STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Herman C. Sehested, 815 Medical Tower, Room 100, 1550 W. Rosedale St., Fort Worth, Tex. 76104. Annual meeting at the Flagship Hotel on Pier, Galveston, Tex.

THE FLEICHNER SOCIETY

Secretary-Treasurer, Eric N. C. Milne, M.B., Medical Sciences Bldg., University of Toronto, Ontario, Canada. Meets in Williamsburg, Va., at the Williamsburg Conference Center, in conjunction with a course on "Modern Trends in Roentgenology of the Chest," sponsored by the Virginia Commonwealth University, Richmond, Va., March 14-18, 1971.
TRI-STATE RADIOLOGICAL SOCIETY

Secretary, Dr. John H. Marchand, Jr., Methodist Hospital, Henderson, Ky. Meets third Wednesday of Oct., Jan., March and May, 8:00 P.M., Elks Club in Evansville, Ind.

University of Michigan Department of Roentgen-OLOGY STAFF MEETING

Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital, Ann Arbor, Mich.

UPPER PENINSULA RADIOLOGICAL SOCIETY Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

UTAH STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. R. Newell Ford, St. Mark Hospital, 803 North 2nd West, Salt Lake City, Utah 84103. Meets fourth Wednesday in January, March, May,

September and November at Holy Cross Hospital. Vermont Radiological Society, Chapter of ACR Secretary, Dr. Edward A. Kupic, Mary Fletcher Hosp., Burlington, Vt. 05401.

VIRGINIA CHAPTER OF ACR

Secretary-Treasurer, Dr. James S. Redmond, Suite 7, Medical Center, Lynchburg, Va. 24501.

Washington, D. C., Chapter of ACR Secretary-Treasurer, Dr. Joan Wohlgemuth, 5021 Seminary Rd., Alexandria, Va. 22311.

WASHINGTON STATE RADIOLOGICAL SOCIETY, CHAPTER OF

Secretary-Treasurer, Dr. Paul S. Paulson, 1001 Broadway Seattle, Washington 98122. Meets quarterly.

WEST VIRGINIA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. J. Dennis Kugel, 510-517 Med. Arts Bldg. Charleston, W. Va. 25301. Meets concurrently with annual meeting of West Virginia State Medical Society; other meetings arranged by program committee. WESTCHESTER COUNTY RADIOLOGICAL SOCIETY

Secretary, Dr. Edgar Palmer, 650 Main St., New Rochelle, N. Y. 10801. Meets on third Tuesday of January

and October and on two other dates.

WISCONSIN RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Robert E. Douglas, 1209 S. Commercial St., Neenah, Wis. 54956. Meets twice a year, May and September.

WYOMING RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. J. D. Grant, Memorial Hosp., Sheridan, Wyo. Meets in fall with State Medical Society and in spring on call of President.

MEXICO, PUERTO RICO AND CENTRAL AMERICA

Asociación Costarricense de Radiología

Secretary, Dr. Jorge Vargas Segura, Apartado 5367, San José, Costa Rica.

ASOCIACIÓN DE RADIÓLOGOS DE CENTRO AMERICA Y PANAMÁ. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá. Secretary-General, Dr. Roberto Calderón, Calle Central Oeste No. 218, Managua, Nicaragua, Central America.

Meets annually in a rotating manner in the six countries. Asociación Puertorriqueña de Radiología Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional

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Secretary, Dr. Pierre Archambault, Hôpital Charle Le Moyne, 121 Boul. Taschereau, Greenfield Park, P.Q., Canada. Meets four times a year.

BRITISH INSTITUTE OF RADIOLOGY

Honorary Secretary, Dr. G. H. du Boulay, 32 Welbeck St., London, W. I, England. Meets monthly from October until May.

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FACULTY OF RADIOLOGISTS

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Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)

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Secretary General, Dr. Guy Duckett, 1385 est, rue Jean Talon, Montréal, P.Q., Canada. Meets every third Tues-

day from October to April.
Toronto Radiological Society

Secretary, Dr. George Wortzman, Toronto General Hosp., Toronto 12, Ont., Canada. Meets second Monday of each month, September, through May.

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Secretary, Dr. Carlos Vildósola, Casilla, 13426 Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia Secretary-General, Dr. Raul Fernández Angula, Calle 43 No. 44-70 Barranquilla, Colombia. Meets last Thursday of each month.

Sociedad Equatoriana de Radiología

Secretary, Dr. Carlos Palau Jimenez, Casilla 4569, Guayaquil, Ecuador.

Sociedad Paraguaya de Radiología

Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

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SOCIEDAD DE RADIOLOGÍA, CANCEROLOGÍA Y FÍSICA MÉDICA DEL URUGUAY

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Sociedad Venezolana de Radiología y Medicina Nu-

CLEAR

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### CONTINENTAL EUROPE

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Société Royale Belge de Radiologie

General Secretary, Dr. Joseph Baeyens, Alost, Belgium. Meets in February, March, May, June, September,

October, November and December.

Société Éuropéenne de Radiologie Pédiatrique President, Dr. George Thomsen, Rigshospitalet (University Hospital), Blegdamsvej 9, DK 2100 Copenhagen, Denmark. Meets in Elseneur, Denmark, May 12-15, 1971.

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and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, du

Nord, DE L'OUEST, DE L'EST, ET D'ALGER ET D'AFRIQUE DU NORD. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France. Secretary-General, Dr. Ch. Proux, 9 rue Daru Paris 8º,

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Germany.

Società Italiana di Radiologia Medica e di Medicina NUCLEARE

Secretary, Dr. Ettore Conte, Ospedale Mauriziano Torino, Italy, Meets annually.

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Secretary-General, Professor C. E. Unnérus, M.D., Hagalung-Tapiola, Havsvindsvägen 5 C., Finland.

Sociedad Española de Radiología y Electrología Médicas y de Medicina Nuclear

Secretary, Dr. D. José Bonnati, Villanueva, 11, Madrid 1, España. Meets every second Friday of each month, Oct. to June, inclusive, in Madrid.

SCHWEIZERISCHE GESELLSCHAFT FÜR RADIOLOGIE UND NUKLEARMEDIZIN (SOCIÉTÉ SUISSE DE RADIOLOGIE ET de Médecine Nucléaire) Secretary, Dr. med. Gustav Schoch, Bethesdaspital. Gellerstrasse 144, 4000 Basel, Switzerland.

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Secretary, Dr. Issa Yaghmai, P.O. Box No. 14-1151, Teheran, Iran. The Society meets on the second Saturday of each month.

### AFRICA

Association of Radiologists of West Africa Honorary Secretary, Dr. S. B. Lagundoya, University College Hospital, Ibadan, Nigeria, Annual Conference: Feb. 5-6, 1971, Conference Centre, University of Ibadan, Ibadan, Nigeria.

SOUTH AFRICAN INTERNATIONAL RADIOLOGICAL CONGRESS Director, Dr. Paul Sneider, P.O. Box 4878, Johannesburg.

South Africa.



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### ROENTGEN DIAGNOSIS

### HEAD

CAMMISA, M. Il cherubinismo: studio di un nucleo familiare affetto da displasia fibrocistica dei mascellari. (Cherubism: study of a family presenting fibro-cystic dysplasia of the jaws.) *Radiol. med.*, April, 1970, 56, 329—341. (Address: Casa Sollievo Sofferenza, S. Giovanni Rotondo, Foggia, Italy.)

Three cases of cherubism are reported and discussed.

The first case, a girl of 6 years of age, came to the observation of her physician because of a slow but continuous swelling of the mandible during the 2 years prior to admission. Once the diagnosis of cherubism was established, other members of the family were examined and a brother, 7 years of age, was found to have the same clinical picture. The mother of the 2 children, aged 28 years, remembered that in her childhood a swelling was noted of her mandible, and that, because the molars never erupted, she was seen by a dentist. Roentgen studies of her mandible clearly showed the retained molars and the presence of sclerotic septa.

The incidence of the disease is not high; the authors found only 91 cases reported in the literature. There is a discrete preference for the male sex (60 per cent of the cases, De Chaume et al., 1962), and the disease is hereditary.

The first clinical manifestations are noted between the second and third year of life. However, the majority of cases have been observed between the third and fourth year. The clinical, roentgenographic, and histologic changes are well known.

The article is well illustrated and the bibliography is up-to-date.—A. F. Govoni, M.D.

### Neck and Chest

Josephson, Staffan. Pulmonary hemodynamics during experimental air embolism: evidence of vasoconstriction. Scandinav. J. Clin. & Lab. Invest., 1970, 26, Suppl. 115, pp. 37. (From: Thoracic Surgery Research Laboratory, Karolinska Sjukhuset, Stockholm, Sweden.)

An experimental model has been devised to study the pathophysiologic mechanisms of pulmonary microembolization for evaluation of contribution from vasoconstriction to the rise of pulmonary arterial pressure in this model and to localize the site of such a vasoconstriction.

The previous literature has been reviewed in detail concerning mechanical obstruction versus vaso-constriction as the cause of pulmonary arterial pressure increase following pulmonary microembolization but the results are controversial.

The results are based on experiments on 72 mon-

grel dogs. The dogs were intubated and anesthetized using sodium pentothal. Sometimes a thoracotomy was performed for placement of intravascular tubes for pressure measurements. At times, blood flow measurements were made in the main pulmonary artery or left lower lobe artery. Pressure measurements were obtained in the main pulmonary artery, aorta, pulmonary arterial wedge, intrapulmonary veins, and left atrium. Pulmonary vascular resistance and systemic vascular resistance were calculated. Pulmonary angiography was performed in some dogs and postmortem examinations were obtained in all dogs. Pulmonary air embolization was performed by means of a catheter in 1 of 4 ways: (1) bilateral embolization; (2) unilateral embolization into one pulmonary artery with free blood flow; (3) unilateral embolization—proximal to a balloon occlusion of one pulmonary artery; and (4) unilateral embolization distal to a balloon occlusion of one pulmonary artery.

On air injection in the main pulmonary artery, the pulmonary arterial pressure rose 140 per cent, the pulmonary arterial wedge and left atrial pressures remained essentially unchanged. The cardiac output decreased 28 per cent and the aortic pressure decreased 9 per cent. All these changes disappeared within 13 minutes. The basal levels of these parameters were not influenced despite manifold repetitions. Repeated embolizations caused similar results with only small variations. Different types of ventilation and breathing gases, and thoracotomy with pulmonary dissection, did not obscure the pattern.

Pulmonary angiograms, made I to 4 minutes after embolization, showed signs of emboli predominantly in the lower lobe, centrally tortuous and widened, peripherally rapidly tapered arteries, a changed pattern of the smallest visible arteries and a shortened artery-to-vein transit time. Repeated angiograms demonstrated a complete normalization after 14 minutes. Angiograms after repeated embolizations exhibited similar changes.

Postmortem examination and microscopy revealed no anatomic lesions, but sometimes a slight edema formation in the lungs, unrelated to length of the experiment, number of embolizations and total doses of air.

Evidence of pulmonary vasoconstriction was found by various techniques of unilateral embolization. On balloon occlusion of one pulmonary artery, only slight modifications appeared. On unilateral embolization, the pulmonary arterial pressure increased 107 per cent. At angiographies, signs of emboli were found only on the embolized side. Nevertheless, centrally tortuous and widened, peripherally tapered arteries were found in the nonembolizing lung. As the mechanical obstruction of the balloon did not entail any marked changes, the considerable effects of unilateral embolization cannot be explained on mechanical grounds alone. A concomitant pulmonary vasoconstriction, also in the contralateral lung, must have been present.

The pressure in small intrapulmonary veins was found to be essentially unchanged after air embolization. As the pressure rise in the pulmonary artery did not depend on flow changes, left ventricular failure or increased pulmonary venous back-pressure, and as pulmonary capillaries are stated to be incapable of active vasomotion, the site of constriction is likely to be on the arterial side of the capillaries.—
W. T. McLaughlin, M.D.

VALK, P. E., MORRIS, J. G., and McRAE, J. Pulmonary embolism as a complication of ventriculoatrial shunt. *Australasian Radiol.*, Aug., 1970, 14, 272–274. (From: Department of Nuclear Medicine, Royal Prince Alfred Hospital, and Department of Medicine, University of Sydney, Australia.)

The authors report a case of septic thromboembolism occurring 2 years after placement of a ventriculoatrial shunt. In their discussion, they note the disparity between the low incidence of clinically apparent pulmonary embolism and the high incidence of pathologic pulmonary embolism at postmortem examination in these patients. Perfusion lung scanning on a routine basis is suggested as a useful means of detecting asymptomatic pulmonary embolism in patients with ventriculoatrial shunts.

Thrombus formation on the outside of permanent transvenous pace-maker catheters, ventriculoatrial catheters and angiographic catheters has been repeatedly demonstrated and has led to renewed interest in developing nonthrombogenic catheter systems.—Robert I. White, Jr., M.D.

LINDSEY, H. E., and WYLLIE, J. H. Release of prostaglandins from embolized lungs. *Brit.* J. Surg., Oct., 1970, 57, 738-741. (From: Department of Surgery, University College Hospital Medical School, London, England.)

It seems clear that nervous or humoral reactions are involved in the production of hypotension, hyperventilation and bronchospasm with the intravenous injection of particulate material and subsequent pulmonary microembolism.

The possibility that emboli release chemicals with a histamine-like effect on "lung-irritant receptors" has been evaluated by experiments involving the embolization of isolated lungs obtained from rats and guinea-pigs. The effluent from the pulmonary veins of these embolized lungs was delivered to isolated tissues including rat stomach strip, rat colon, and guinea-pig ileum. The responses of the tissues were recorded on a smoked-paper kymograph by frontal writing levels. The perfusion pressures and temperatures were monitored and controlled. The perfusion fluid consisted of Krebs' solution gassed with 5 per cent carbon dioxide and oxygen. The substances injected into the lungs were various fat

emulsions, suspensions of microspheres, and a colloidal suspension of iron-dextran complex. Some of the injected particles caused a release of pharmacologically active material from the lungs and the nature of the material was investigated by pharmacologic tests, extraction, chromatography and bioassay. The testing procedures are described in detail.

In a typical experiment, prosparol was injected into the stream of Krebs' solution superfusing the rat stomach strip. A dose of 50 mg. of this fat caused no contraction of the strip, but when the same dose was injected into the lungs the effluent from the pulmonary veins caused a prolonged contraction of the rat stomach strip.

The activity released by the lung was equivalent to more than 40 ng. of prostaglandin E-2. Prostaglandins are released from guinea-pig lungs in anaphylaxis and also when the lungs are artificially distended. Multiple detailed experiments were performed to show that they are also released when the lungs are embolized. The possibility that other substances may also be released has not been completely evaluated.

Multiple experiments were performed with particles of varying size and it appeared that particles had to be larger than I micron in diameter to release prostaglandins from the lungs.

It is believed that prostaglandin release is a biologic phenomenon because the test tissues did not respond till about I minute after the prosparol had reached the lungs; and the embolized lungs did not release activity when cooled to 6° C. Feeble release of activity did occur after re-warming of the lungs.

It is not known whether prostaglandin release serves any useful purpose or whether it is merely an expression of cell damage. E type prostaglandins have a vasodilator action and they may contribute to the fall in systemic blood pressure after pulmonary embolization. It is possible that when prostaglandin antagonists are developed, a possible use for them would be in mitigating the pharmacologic consequences of pulmonary embolization.—W. T. Mc-Laughlin, M.D.

### SKELETAL SYSTEM

Bragg, David G., Shidnia, Homayoon, Chu, Florence C. H., and Highbotham, Norman L. The clinical and radiographic aspects of radiation osteitis. *Radiology*, Oct., 1970, 97, 103–111. (From: Departments of Diagnostic Radiology, Radiation Therapy and Bone Service, Memorial Hospital for Cancer and Allied Diseases, and Cornell University Medical College, New York, N. Y.)

The emphasis in this article is upon the roentgenographic appearances of radiation osteitis and the findings which may help distinguish this from metastatic involvement and from radiation induced tumors. The authors conclude that the lethal effects of irradiation upon osteoblasts and osteoclasts are involved in the evolution of radiation osteitis as well as in the decreased ability of irradiated bone to respond to trauma or infection. Changes in the vascular bed, the less rapid metabolic turnover of bone, and the inability of osseous tissue to develop collateral circulation, all influence the process which apparently occurs up to 5 years after a dose of about 5,000 r. It is less common since the advent of supervoltage therapy, but it still exists especially with excessive total dose, repeated treatment courses, overlapping fields, and orthovoltage modality.

Nearly every section of the skeleton was involved in the 100 patients studied, although the vertebral column, excluding the sacrum, was seldom affected. Open wounds and fractures complicated the radiation osteitis and treatment frequently necessitated amputation or complete excision. Correct diagnosis, however, may sometimes prevent a needless amputation.

Diffuse areas of increased density may be seen in radiation osteitis of the pelvis, but bone demineralization was probably the most common feature elsewhere; it was associated with coarsening or disorganization of trabeculae often of a "Pagetoid" nature. Lack of symptoms even in the presence of rib fractures was common. Pain may occur, however, with fracture of a weight bearing bone. Lack of roent-genographic change after 5 years in the absence of fracture or infection is the usual situation (superimposed infection leads to rapid progression of bone lesions and soft tissue calcification).

In the absence of fracture or infection, the following roentgenographic features suggest radiation induced sarcomas: resorption or disintegration of a bone (only in the distal fragment of a fractured clavicle was resorption and dissolution found in the absence of malignancy or infection); soft tissue mass; sudden change in appearance of a bone more than 5 years after irradiation; presence of disorganized bone; and soft tissue calcification.

In the absence of fracture or infection the following features suggest bone metastasis: symptoms associated with the lesion; presence of bone destruction; and focus outside of the irradiated area.—L. M. Nikolai, M.D.

### BLOOD AND LYMPH SYSTEM

KIRSCHNER, LOUIS P., TWIGG, HOMER, and FARKAS, JOHN. Drip infusion venography. Radiology, Aug., 1970, 96, 414-415. (From: Department of Radiology, Commonwealth Doctors Hospital, Fairfax, Va., Department of Radiology, Georgetown University School of Medicine, Washington, D. C., and Department of Radiology, Washington Hospital Center, Washington, D. C.)

The authors present a modification of the generally used venographic technique, termed drip infusion venography, and describe its roentgenographic and diagnostic advantages. In this method the contrast medium is introduced by continuous intravenous drip infusion, as opposed to the customary bolus injection. While this method can be used in all the extremities, the present discussion is concerned only with the examination of the venous network of the legs.

A 60 per cent solution of methylglucamine diatrizoate may be used, diluted I:I with normal saline, but the recently available infusion kit with 30 per cent methylglucamine diatrizoate is recommended, along with the thin walled 21 gauge needle infusion set. From 300 to 400 ml. of the solution is injected into a suitable vein on the dorsum of the foot. After a preliminary roentgenographic exposure, the patient is tilted between 35° and 50° from the horizontal, and the infusion is started at a fast drip rate. A tourniquet is then applied above the ankle or at the inguinal region, depending on whether the deep or superficial venous system is to be visualized. The first exposure is obtained after 75 to 100 ml. of the solution is infused and further roentgenograms are taken as desired. The rapid drip infusion is continued until the contrast solution is exhausted or all the desired views are obtained.

The authors state that venographic studies, especially in the legs, are indicated for venous incompetence without apparent cause, a previous history of venous thrombosis, thrombophlebitis, varicose veins, the post-thrombotic syndrome, and in instances of chronic swelling and skin changes secondary to venous stasis with little or no external evidence of superficial vein incompetence. The contraindications include acute deep vein thrombosis, cellulitis, arterial insufficiency and hypersensitivity to the contrast medium.

Drip infusion venography is suggested as a new approach to the visualization of the venous channels of the extremities. The procedure is simple and good venograms may be obtained in 20 to 30 minutes.

The authors find this method superior to the customary bolus injection method, because it gives a continuous uniform visualization of the venous channels, permits unhurried and optimal views of the area, and will even allow positional fluoroscopy. A tourniquet applied to the ankle results in outlining of the deep veins and, with an inguinal tourniquet, both the deep and superficial venous systems are visualized.—Edward B. Best, M.D.

### GENERAL

RITCHIE, WALLACE P., JR., ERSEK, ROBERT A., BUNCH, WILTON L., and SIMMONS, RICHARD L. Combined visceral and vertebral injuries from lap type seat belts. Surg., Gynec. & Obst., Sept., 1970, 131, 431-435. (From: De-

partments of Surgery and Orthopedics, University of Minnesota Medical School, Minneapolis, Minn.)

Four cases are reported, representing a common constellation of injuries to occupants wearing lap type seat belts in a high speed motor vehicle accident. The 4 patients are members of a family involved in a head on collision at 50 miles an hour. All were wearing standard lap type seat belts.

The mother, age 35, and a daughter, age 11, sustained fractures of the 2nd and 3rd lumbar vertebrae, respectively. The transverse fractures involved the posterior spinous process, extended on the laminae bilaterally through the pars interarticularis, involved both transverse processes as well as both pedicles, and extended on to the body of the vertebra. There was no displacement. Both required spinal fusion.

Because of increasing abdominal rigidity, absent bowel sounds and elevated white blood cell count, exploratory laparotomy was performed. The mother sustained a circumferential serosal tear at the midjejunal level, a punctate laceration of the proximal portion of the ileum, and a longitudinal serosal tear of the hepatic flexure of the colon. The daughter had a circumferential transection of the proximal ileum, a serosal tear of the ileum and a rent in the mesentery of the ascending colon. Both recovered uneventfully following appropriate surgical repair.

The 7 year old daughter received a fracture of the right lamina of the third lumbar vertebra which extended into the pars interarticularis and through the pedicle on the right side. She was placed in a cast and no fusion was required.

The father sustained no lumbar vertebra fracture, but had 2 separate transections of the terminal ileum. He also recovered.

The mechanism of both the vertebral and visceral injuries apparently is an acute hyperflection and rapid deceleration about the restraining transverse seat belt. Solid organ injury is infrequent, except when the belt has been improperly worn.

Delay in diagnosis of the intraabdominal injuries is quite common and contributes to mortality. A major factor contributing to delay may be that the signs of peritoneal irritation, if present, are attributed to reflex ileus resulting from coexisting lumbar vertebral fracture.—David Morse, M.D.

RIGGS, WEBSTER, JR. Roentgen findings in Noonan's syndrome. Radiology, Aug., 1970, 96, 393-395. (From: Department of Radiology, University of Tennessee College of Medicine and LeBonheur Children's Hospital, Memphis, Tenn.)

The term Noonan's syndrome has recently been applied to patients with short stature, delayed puberty, hypertelorism, congenital heart disease, mental retardation, and normal chromosomal analysis.

The roentgenographic findings include: sternal deformity, congenital heart disease, mandibular hypoplasia, hypertelorism, retarded bone age, variable skull abnormalities, and urographic abnormalities such as pyelectasis and duplication.

The above findings are based on a review of the rather complete roentgen evaluation of II cases of Noonan's syndrome.

Noonan's syndrome patients differ from patients with Turner's syndrome, since they show a normal chromosomal analysis, less consistent growth retardation, and a greater incidence of mental retardation and pulmonic stenosis. The condition occurs in both males and females, and there is some evidence that Noonan's syndrome may be a familial disorder.—
G. E. Kim, M.D.

Gupta, S. K., and Srivastava, T. P. Pyle's disease. *Indian J. Radiol.*, Feb., 1970, 24, 46–49. (Address: Dr. S. K. Gupta, Reader in Radiology, College of Medical Sciences, Banaras Hindu University, Varanasi, India.)

A case of Pyle's disease in a 7 year old child is reported. The entity is also known as craniometaphyseal dysplasia. It is attributed to failure of absorption of a secondary spongiosa of the bone. This disturbs the modeling of bones, particularly the long bones. The circumference of the bone is generally larger than normal. There is thinning of the cortex, especially at the metaphyses. A genu valgum deformity is usually present.

Sporadic cases have been reported previously with involvement also of the flat bones. The sternal end of the ribs may show splaying. The pelvis may be deformed with widening and cortical thinning of the pubic and ischial bones, narrowing of the transverse diameter of the pelvic inlet and obturator foramen. The clavicle and mandible may also show expansion. Cranial changes described in association with this disease include: sclerosis of the vault; leontiasis ossea; absence of aeration of the mastoids and paranasal sinuses; and sclerosis of the orbital ridges.— Saul Heiser, M.D.

Gokiert, J. Guy, and Beamish, W. E. Altered reactivity to measles virus in previously vaccinated children. *Canad. M. A. J.*, Oct., 1970, 103, 724–727. (Address: J.GuyGokiert, M.D., 5682 Victoria Street, Vancouver, British Columbia, Canada.)

Exposure to natural measles within 2 to 4 years in children vaccinated with killed measles vaccine can result in a clinical syndrome of altered measles reactivity.

The authors report 51 children admitted to hospital with the atypical measles illness, who had received their last killed measles vaccination 27 to 45 months before exposure to mild measles virus during a small epidemic of measles in Edmonton, Alberta.

The atypical measles illness consists of a prodromal cough and high fever followed by a maculopapular rash appearing on the extremities and progressing centripetally. In the cases reported, pulmonary consolidations with or without pleural effusions were evident, but apparently cleared rapidly in 4 or 5 days. No mention is made of any long term follow-up.

Although initial leukocyte counts and sedimentation rate values suggested a bacterial etiology, no pathogens were isolated. The authors show that complement fixation titers for measles were present in acute and convalescent sera indicating a definite measles infection.

The purpose of the paper is to point out the possibility of an altered measles reaction to measles virus occurring in children receiving killed measles vaccine and to urge that the use of the vaccine be discontinued.—Lionel W. Young, M.D.

CRAIG, MICHAEL W., DAVEY, WINTHROP N., and GREEN, ROBERT A. Conjugal blastomycosis. Am. Rev. Resp. Dis., July, 1970, 102, 86–90. (From: Department of Internal Medicine, Medical Chest Division, University Hospital; and Veterans Hospital, Ann Arbor, Mich.)

The report is concerned with a husband with disseminated blastomycosis, and a wife who acquired the disease through conjugal relationship. The male had diffuse bilateral pulmonary parenchymal infiltrations, thought initially to represent tuberculosis. He developed prostatitis, right epididymitis and testicular swelling. A transurethral resection and removal of the right testicle and epididymis were done. The histology showed granulomas and organisms typical of Blastomyces dermatitidis. Cultures of the epididymis yielded B. dermatitidis as did urine cultures preoperatively. About the time the husband developed epididymal swelling, the wife had onset of abdominal cramps, chills and fever. Surgery was performed with excision of a tubo-ovarian mass. Subsequently an abdominal hysterectomy was performed. Histologic examination revealed granulomatous infection of the endometrium, fallopian tubes and peritoneum. Employing a special stain, the blastomycosis organism was identified.

This is the first reported case of blastomycosis transmitted by sexual intercourse.—Saul Heiser, M.D.

### RADIATION THERAPY

DISIMONE, ROBERT N., EL-MAHDI, ANAS M., HAZRA, TAPAN, and LOTT, STEWART. The response of Stewart-Treves syndrome to radiotherapy. *Radiology*, Oct., 1970, 97, 121–125. (From: Department of Radiology,

The Johns Hopkins Hospital, Baltimore, Md.)

Three cases of lymphangiosarcoma in lymphedematous extremities following radical mastectomy (Stewart-Treves syndrome), including the first 2 reported in Negroes, are reported. Two of the patients received postmastectomy radiation therapy.

Onset of lymphangiosarcoma was 18 months, 7.5 years and 15 years following mastectomy.

The tumor mass in Case I disappeared following 3,500 rads tumor dose orthovoltage radiation; however, she died of liver metastases I year later. The initial lesion in Case II occurred on the anterior chest wall and was treated, without biopsy, as recurrent breast cancer. She received 7,000 rads orthovoltage therapy without any clinical or pathologic response. Case III is alive 8 months following treatment by amputation of the arm.

Although radiation therapy may offer palliation, radical surgical resection appears to be the treatment of choice.—William H. Roush, M.D.

Brascho, Donn J. Use of pelvic pneumography in planning radiotherapy of endometrial carcinoma. *Radiology*, Oct., 1970, 97, 113— 120. (From: Department of Radiation Therapy, University of Alabama Medical School, Birmingham, Ala.)

Radiologists recognize the value of individualized treatment planning and emphasize the importance of describing radiation programs in units of radiation absorption. Attempts have been made to convert radiation treatment techniques expressed in milligram-hours to gamma rads. This has the problem of determination of the location and extent of invasion in endometrial carcinoma. The use of high-dose irradiation of the entire body of the uterus has been recommended, but this has the problem of accurate determination of uterine size. Before radiation treatment can be expressed as an absorbed dose in rads within the myometrium or on the serosal surface, the actual uterine size must be known. Unfortunately, current methods of determining uterine size are often unsuccessful.

Pelvic pneumography is a simple roentgenographic method of demonstrating the pelvic organs and can be used to determine uterine size for radiation treatment planning. In this study, a gas, usually nitrous oxide, is introduced into the peritoneal cavity which outlines the organs of the pelvis. Variations of normal anatomy or previously unsuspected disease within the pelvis may be revealed as well as the usual uterine size, configuration and relationship to adjacent pelvic viscera.

The examination is easily performed in the Department of Diagnostic Radiology, using equipment normally available. It is safely performed on outpatients, the only preparation being a cleansing enema. The patient is kept recumbent for 30 minutes to 1 hour following the procedure.

To determine the actual uterine size, corrections must be made for magnification of the image on the films. The magnification factor is different for each projection and is determined by the method of similar triangles using the measurements recorded at the time of filming. These include the roentgenographic source-to-film distance, the patient thickness and the distance of the film from the patient. The radiologist is able to utilize the information furnished by pelvic pneumograms to plan and individualize the treatment program for the patient with adenocarcinoma of the uterus. He can select the type of radium application most suitable for the uterine size.

After radium insertion, roentgenograms of the pelvis are obtained with contrast medium localizing the rectum and bladder. Then the dose rates at various points of interest may be determined including the serosal surface of the uterus, the myometrium 2 cm. from the uterine axis and the points of greatest radiation intensity to the rectal and bladder mucosa. Also, the dose rate on the superior-posterior serosal surface of the uterus is calculated, as a loop of small bowel may lie here.

A policy of treatment based on general principles of irradiation-planning for other malignant conditions is utilized in which the maximum safe dose to the nearby sensitive structures is the limiting factor. The dosage within the area of the tumor is determined from this information. The key in this treatment situation is knowing the uterine size and the relative position of the other pelvic viscera.

The size of the uterus in the majority of patients with adenocarcinoma is 5 to 7 cm. in transverse diameter and 3 to 5 cm. in anteroposterior diameter. In this situation, it is usually possible to deliver 6,000 rads at a radius of 2 cm. from the uterine axis without exceeding a dose of 4,500 rads to the closest loop of bowel. Occasionally, the uterus is fixed in an anterior anteverted position and as a result the bladder may be the critical organ. In a large uterus containing anaplastic tumor, the dose rates are considered deeper in the myometrium. Also, the presence of myomata causing uterine enlargement must be taken into consideration. In the patient with a small uterus (less than 5 cm.), 6,000 rads 2 cm. from the uterine axis may be excessive and the normal tissue tolerance of the nearby sensitive organs dictates the treatment plan in these cases.

There has been criticism of previous attempts to estimate and standardize the gamma rad dose to the uterus in the treatment of endometrial carcinoma. However, it has been shown that carefully planned and standardized therapy has produced a significant improvement in 5 year survival rates. Because of the potential value of individualized treatment-planning, pelvic pneumography should be adopted as a routine procedure in establishing intracavitary irradiation programs for adenocarcinoma of the uterine fundus.— F. R. Jenkins, M.D.

HATFIELD, PHILIP M., and Schulz, MILFORD D. Postirradiation sarcoma: including 5 cases after x-ray therapy of breast carcinoma. Radiology, Sept., 1970, 96, 593-602. (From: Department of Radiology, Massachusetts General Hospital, Boston, Mass.)

Radiation induced malignant neoplasms have been a concern from the inception of the "radiation era." Malignancies have been observed to develop in all human tissues following irradiation. Postirradiation osteosarcoma, however, has been observed uncommonly. Since 1922 only 150 cases have been reported in the literature.

It has been stated that refinements in radiation therapy have markedly reduced the hazard of post-irradiation sarcoma. The authors wish to emphasize that such tumors still occur. Reported are 11 new cases that have been seen at the Massachusetts General Hospital in the last 15 years. These cases are well illustrated with appropriate roentgenographic reproductions and completely summarized in a single table.

Two aspects are unique: (1) the number of cases that occurred after radiation therapy for cancer of the breast; and (2) the number of cases that followed megavoltage treatment.

Five cases of postirradiation sarcoma occurred after treatment for primary carcinoma of the breast. Because only 6 such cases had been previously reported, it strongly suggests that this is not a disappearing phenomenon.

Three cases of postirradiation sarcoma occurred after primary treatment with megavoltage modalities. This equals the number of cases previously reported in the literature. Although uncommon, it points out that the use of megavoltage therapy does not prevent such a complication.

In addition to these observations, the authors noted the following:

Efforts to correlate the length of the latent period with the initial dose of radiation were unsuccessful. The effects of chemotherapeutic agents or trauma upon induction of postirradiation sarcomas in the latent period are presently unknown, while radiation factors such as energy source and method of delivery appear to have no effect.

A patient with a primary malignancy has a greater risk of developing a second, unrelated neoplasm than the population at large. The second neoplasm statistically occurs sooner than postirradiation sarcoma. This tends to invalidate spontaneous occurrence as the etiology of the latter. In addition, it is noted that postirradiation sarcomas occur with a higher frequency than spontaneous bone sarcomas.

The induction of postirradiation sarcomas in animals has been frequently observed. There is

some variation produced by fractionating the irradiation.

It is concluded that although osteosarcomas are rare in the general population, they occur more commonly in patients who are long term survivors following radiation therapy. Postirradiation sarcomas are a genuine hazard that persists even today in the era of megavoltage therapy.—P. M. Kroening, M.D.

KREBS, ADOLPH T. Bubble chamber pictures as a means of demonstrating radiation distribution in biological systems. *Radiology*, Sept., 1970, 96, 635–638. (From: Radiation Center, University of Louisville Medical School, Louisville, Ky.)

Analysis and visualization of tracts of high energy radiation in tissue directly have to date not been achieved.

Attempts to visualize such tracts in tissue have been based on the assumption that radiation energy in the form of ions, ion pairs, ion clusters is deposited the same in gases as in liquids (allowing for the difference in density between gas and liquid). Cloud chamber pictures combined with photomicrography have been used experimentally, based on the above assumption to demonstrate high energy radiation tracts in gas and relating them then to tissue. However, there has been some question whether the deposition of radiation energy in liquids and gases is actually the same.

The advent of the bubble chamber offers a further means of demonstrating particle paths, in liquids rather than gases. In the bubble chamber, well defined bubbles are formed along the path of the beam and a montage of such paths can be superimposed upon a photograph of a biologic object. In such a manner, the range and distribution of electron tracts and their random properties are demonstrated.

Two such examples are shown. No consideration was made for differences in density between muscle, bone and cartilage in the examples.—I. Whitfield Carhart, M.D.

### RADIOISOTOPES

ATKINS, H. L., FAIRCHILD, R. G., and ROBERTson, J. S. Comparison of irradiation by californium 252 and radium on the skin of swine. *Radiology*, July, 1970, 96, 161–165. (From: Medical Research Center, Brookhaven National Laboratory, Upton, L. I., N. Y.)

As 3.1 per cent of the decay of californium 252 (Cf<sup>262</sup>) is by spontaneous fission giving off fast neutrons, this radionuclide has been considered for implant therapy and sources obtained (see also *Radiology*, 1970, 96, 171–174). Preclinical testing was necessary to assess the RBE of normal tissue in response

to this new modality. Experience with acute radiation by fast neutrons had led to an assumed RBE of 3. Since swine skin and human skin exhibit similar tolerance to radiation, swine were selected as test subjects. A 6×6 cm. surface applicator containing Cf252 delivering a dose of 12-13 rads/hr. and another of equal size, containing Ra226 delivering a dose of 35 rads/hr. were applied to the animals' shaved skin. The source-to-skin distance of the 2 applications varied: 5 mm. for Cf25 and 6.5 mm. for radium. This resulted in a variance in uniformity of the irradiated field. The skin of various animals was irradiated to progressively higher total doses, but in all situations the dose from radium was 5 times that of californium. After removal of the applicators the irradiated areas were observed for up to 100 days for reactive changes.

Reactions were graded according to the methods of previous investigators and classified as: (0) none; (1) mild erythema; (2) severe erythema; (3) dry desquamation; (4) moist reaction, less than 50 per cent of the irradiated field; and (5) moist reaction, more than 50 per cent of the irradiated field. No consistent pattern could be seen through the first 4 classifications. In the fifth classification the results were obtained with about 1,140 rads (Cf<sup>220</sup>) and 6,000 rads (Ra<sup>220</sup>). Moist reactions occurred between 10–21 days. With one minor exception the lesions produced in the sixth classification failed to heal in 50 days after the applicators were removed.

The levels of exposure to cause this were: 1,725 rads (Cf<sup>282</sup>), and 8,400 rads (Ra<sup>203</sup>). The RBE is 5.3 and 4.9 respectively, in these latter 2 classes. The regrowth of the shaved hair was also evaluated and an RBE for Cf<sup>282</sup> in the range of 5.7–7.2 was determined.

The authors' previous work with exposure of HeLa cells in culture led them to believe that the RBE of Cf<sup>262</sup> was approximately 3, and they designed their experiment so. This causes certain inequities in procedure such as requiring 10 days of exposure by radium to achieve the same results as 6 days of californium exposure.

The authors believe that the increasing dose rate of Cf<sup>122</sup> will not materially affect the skin tolerance level, and that RBE values are dependent on the dose rate of the gamma irradiation to which it is being compared.—F. C. Petty, M.D.

Bushong, Stewart C., Prasad, Naresh, Briney, Sharon A., and Oliver, George D. Radiocytogenetic determination of the oxygen enhancement ratio of californium 252. Radiology, July, 1970, 96, 167–170. (From: Department of Radiology, Baylor College of Medicine and the Department of Physics, University of Texas M. D. Anderson Hospital and Tumor Research Institute, Texas Medical Center, Houston, Texas.)

Californium 252, a by-product of the United States Atomic Energy Commission's transplutonium isotope production program, has recently been made available for evaluation in medical and industrial applications. Cf<sup>282</sup> has a half life of 2.65 years and undergoes spontaneous fission yielding 2.34×10<sup>5</sup> neutrons and 1.3×10<sup>7</sup> photons per second per microgram.

This isotope is being considered as a possible replacement for radium 226 in radiotherapy. Cf<sup>262</sup> offers promise of successful treatment in radiotherapy failure with Ra<sup>266</sup>. These failures are believed to be due to the hypoxic cells in some lesions being far more resistant to the gamma radiation of Ra<sup>266</sup> than are oxygenated cells. There appears to be little difference between oxygenated and hypoxic cells in terms of radiosensitivity to fast neutron irradiation. The authors have determined the oxygen enhancement ratio (OER) based upon the cytogenetic effects of Cf<sup>266</sup> irradiation of mammalian cells.

Cultured Chinese hamster cells were suspended in plastic tubes containing I ml. of Puck's saline solution A. One lambda of Dow Corning Anti-Foam A was added to each suspension which was then aerated with a gas mixture of either oxygen containing 5 per cent CO<sub>2</sub> or prepurified nitrogen containing 5 per cent CO<sub>2</sub> for 15 minutes before and during irradiation.

The tube containing the suspension was placed in the center of a polystyrene phantom to simulate a tumor environment. Four sources (1.5 cm. active length, applicator tube-type) of Cf<sup>220</sup> were placed concentrically around the cell suspension, whose center was 9 mm. from the center of the sources.

The gamma dose rate was 25.1 rads per hour and the neutron dose rate was 35.3 rads per hour, yielding a neutron-to-gamma ratio of 1.41.

The OER of this system was 1.75. The aerobic and anaerobic aberration frequency was 0.0135 and 0.0077 single-hit chromosome aberrations per cell per rad, respectively. On the basis of this study, it appears that Cf<sup>262</sup> irradiation results in a lower OER than does photon irradiation and therefore should be more effective than Ra<sup>225</sup> in the treatment of malignant disease.—John Hutka, M.D.

### **CHEMOTHERAPY**

Working Party on Tumours in Childhood. Moderator: U. Köttgen (Mainz); Participants: K.-D. Bachmann (Cologne), L. Diethelm (Mainz), H. Dowe (Krefeld), L. Horbach (Mainz), U. Keuth (Neunkirchen), W. Luboldt (Essen), J. Michaelis (Mainz), H. Müller (Bethel), M. Neidhardt (Mainz), H. Ohm (Brunswick), P. Sachtleben (Homburg), G.-W. Schmidt (Giessen), W. Welte (Cologne-Riehl), and H. Willmanns (Brackwede). Malignant tumours in childhood: results of a co-operative therapeutic study with cyclophosphamide and radiotherapy. German Med. Monthly, Aug., 1970, 15, 433-438. (Address: Priv.-Doz. Dr. M. Neidhardt, Universitäts-Kinderklinik, Langenbeckstrasse 1, 65 Mainz, Germany.)

Comparison was made between the results of treatment in 2 consecutive series of malignant tumors in children. The first series (282 patients) was mainly treated in the precytostatic era by operation and irradiation, while the second series (383 patients) was treated with cyclophosphamide, in addition to operation and irradiation, in accordance with an established treatment schedule. The tumors treated were of the central nervous system, neuroblastoma, Wilms' tumor, malignant lymphomas and others.

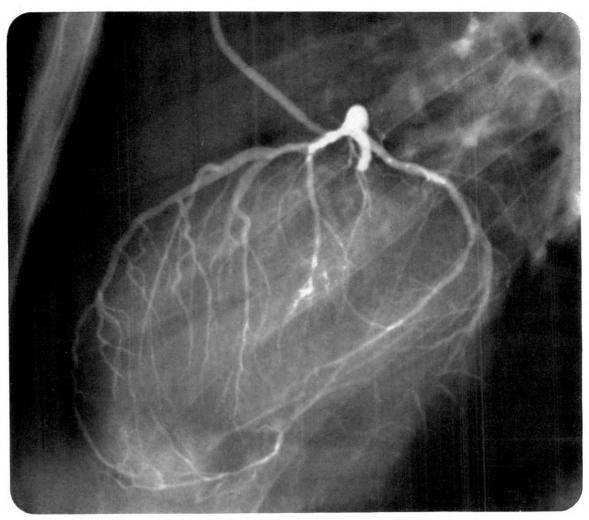
In both series treated, a large number of patients died during the year following diagnosis. However, the addition of cytostatic therapy in the form of cyclophosphamide resulted in a significant prolongation of survival time in the first year. Radiotherapeutic technique improvements also played a part. The proportion of permanent cures was better in neuroblastomas and Wilms' tumors than in medulloblastomas and lymphosarcomas or reticulum cell sarcomas. Additional chemotherapeutic agents employed were: actinomycin D used for Wilms' tumor. and a combination of cyclophosphamide and vincristine for neuroblastoma. A superiority of cyclophosphamide treated cases beyond 2 years from diagnosis was not observed in any of the groups classified according to diagnosis or tumor stage. In both series a survival of more than 2 or 3 years corresponded in practice to a cure.

The report constitutes a cooperative therapeutic study, utilizing 9 different institutions and the results date up to 1968.—Lionel W. Young, M.D.



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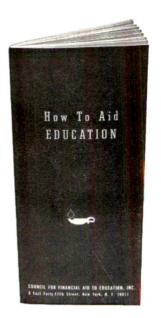
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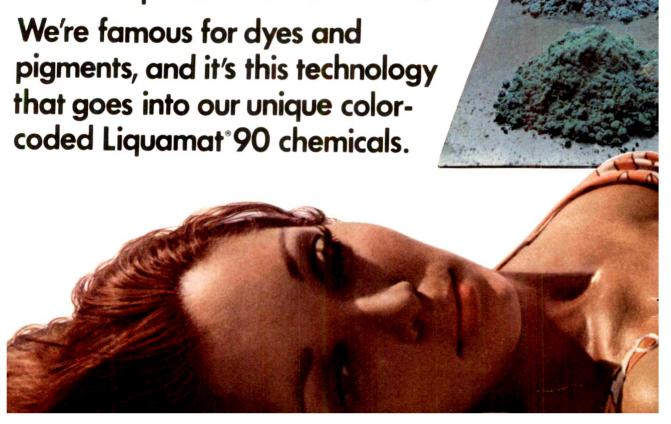
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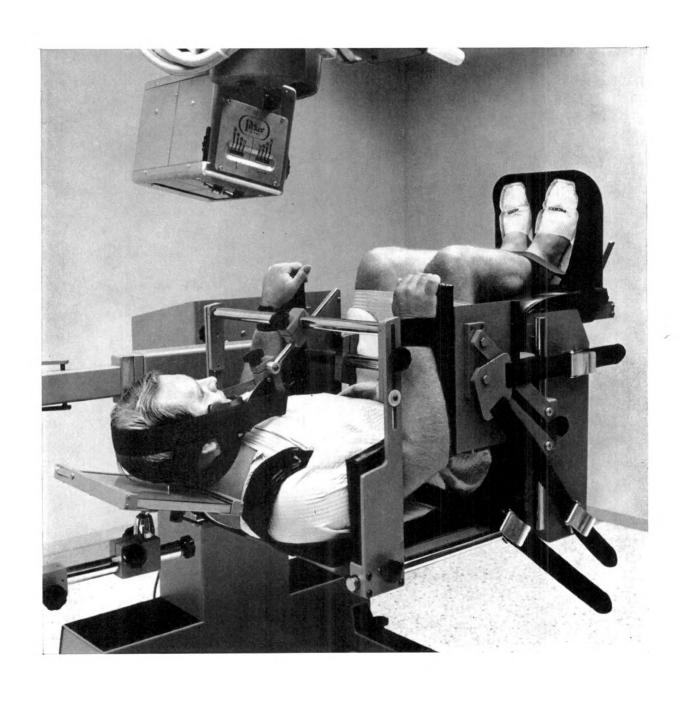
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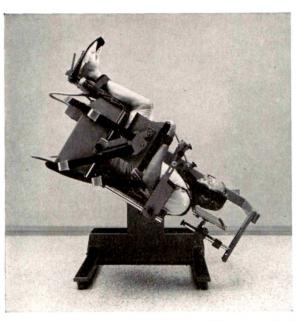
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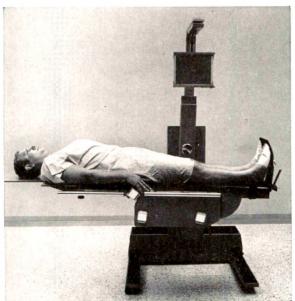


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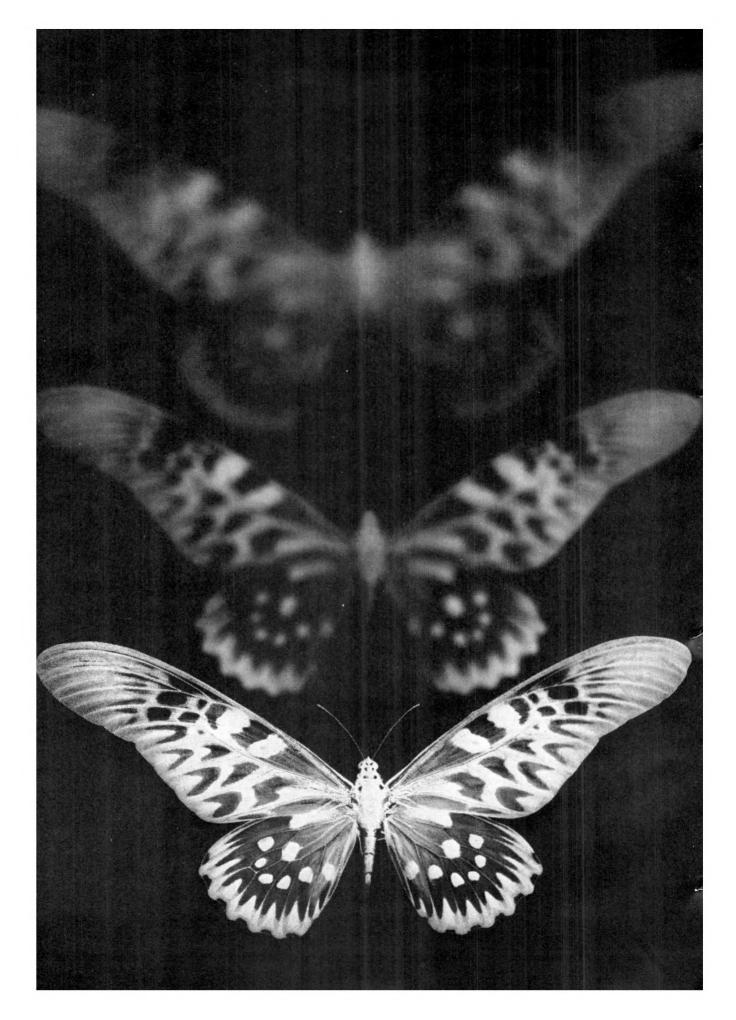


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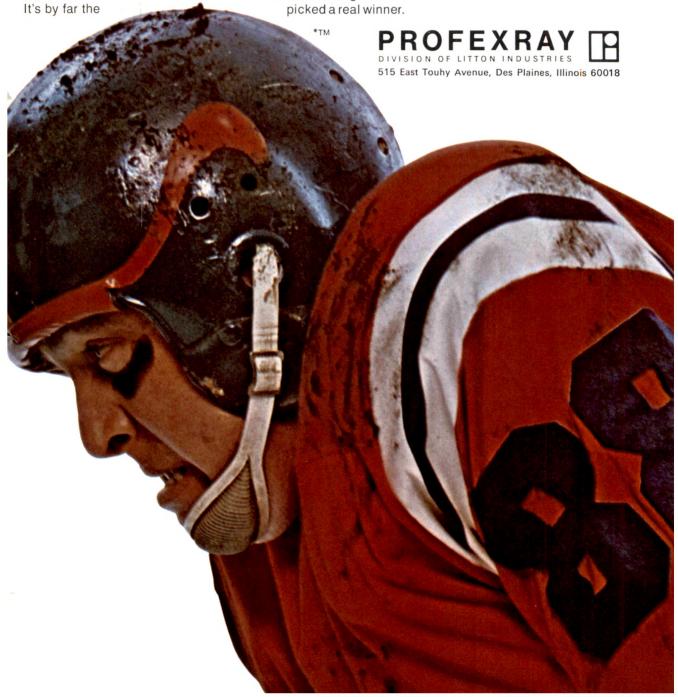
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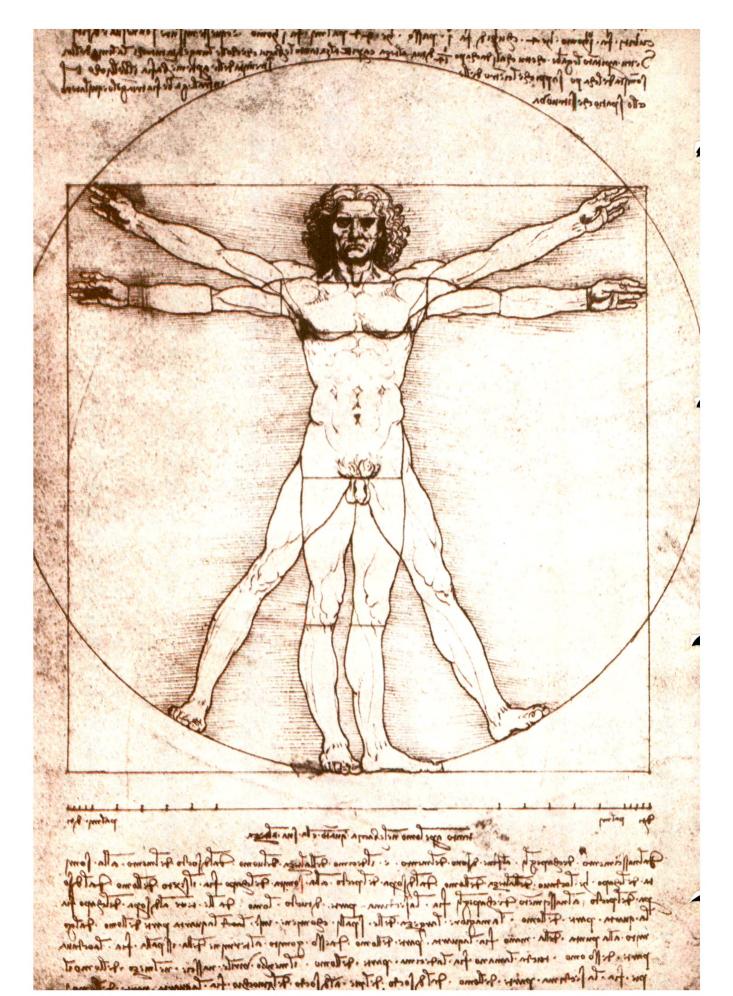
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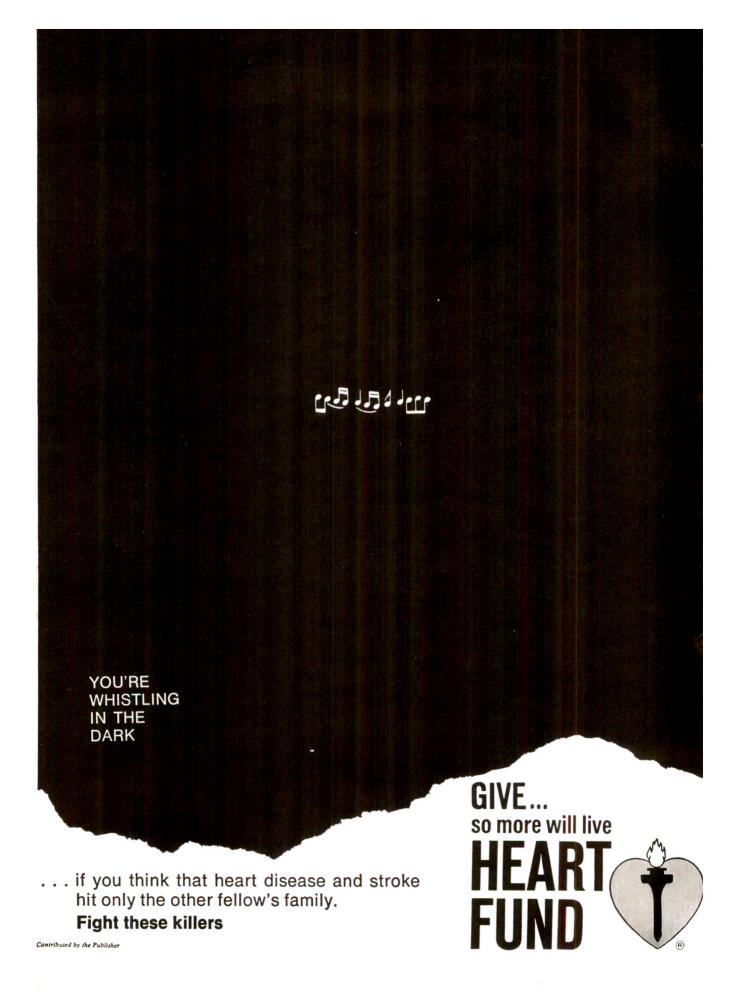
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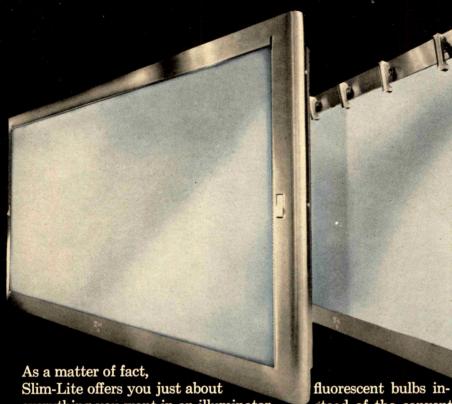
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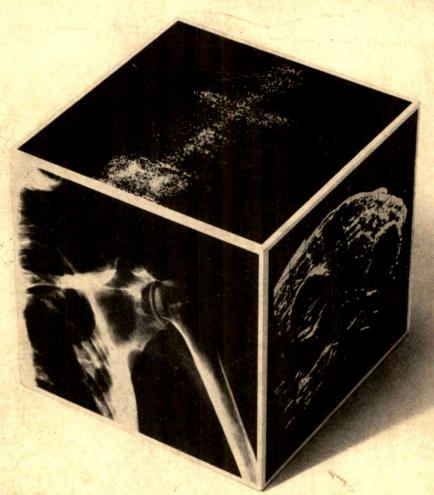
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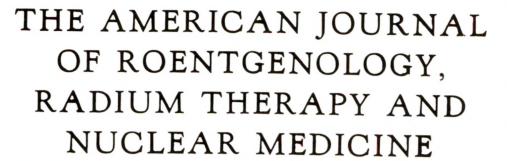
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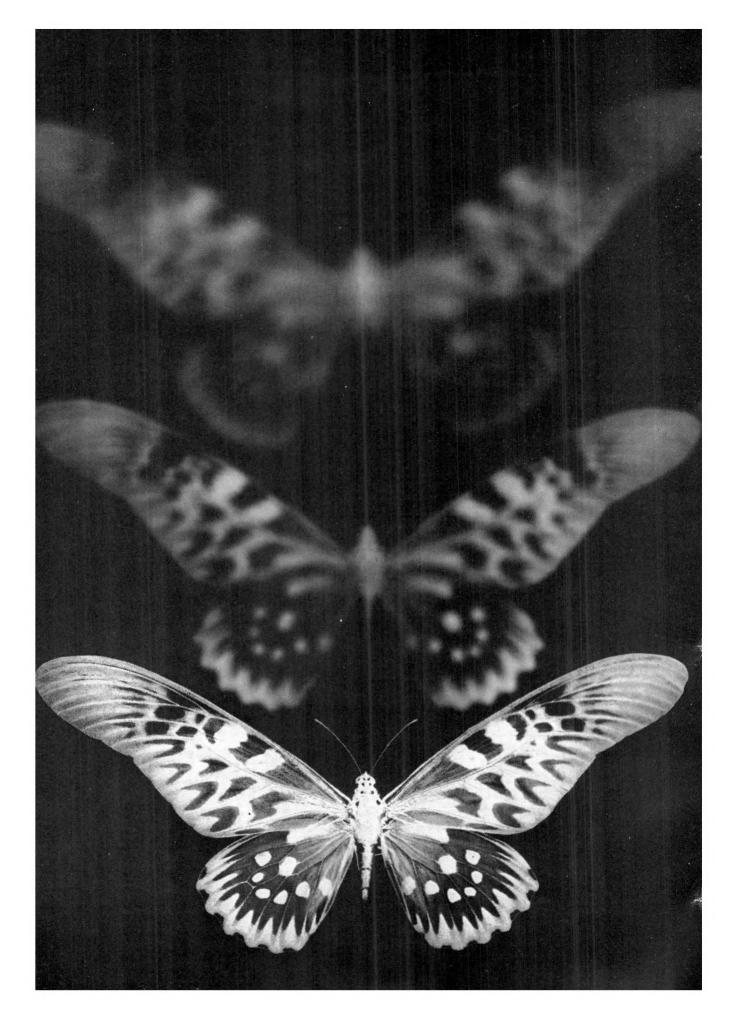
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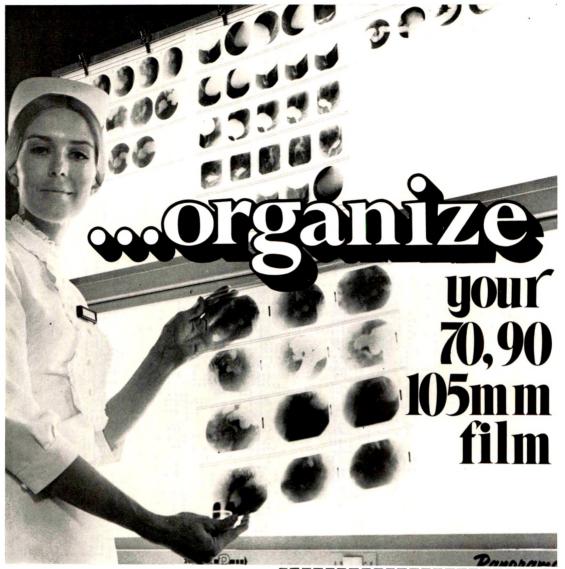
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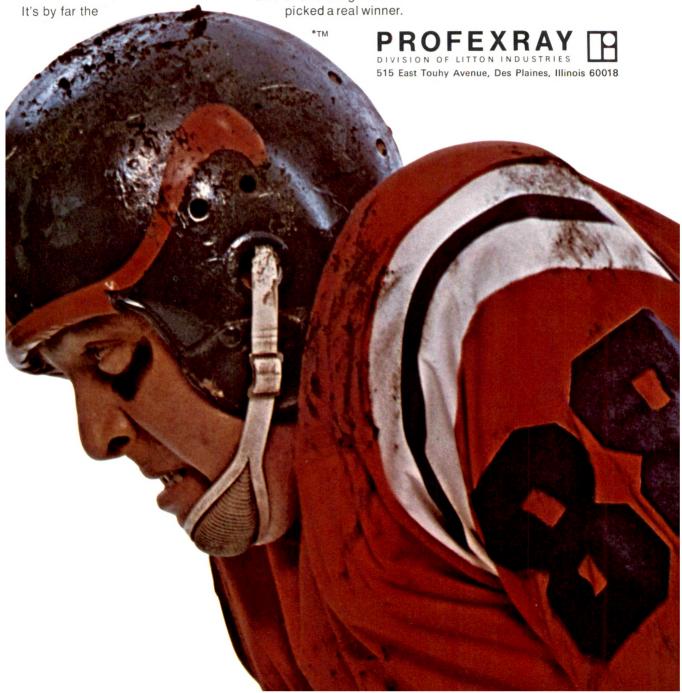
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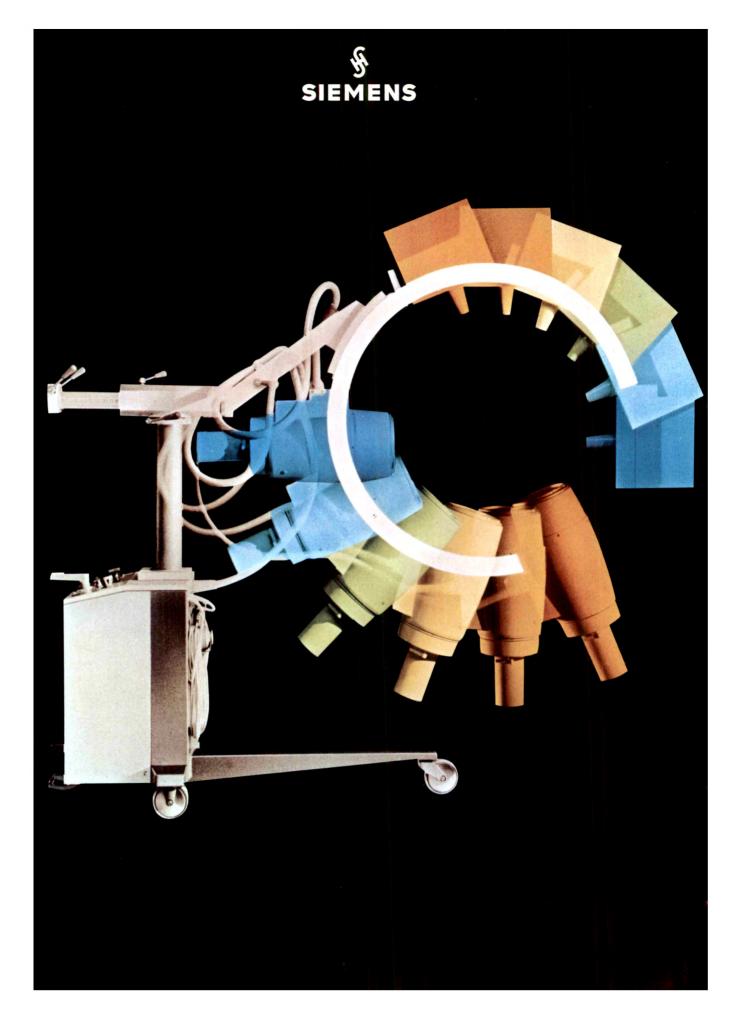
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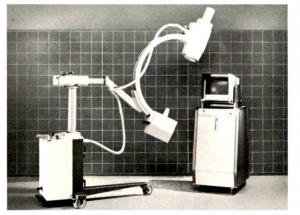
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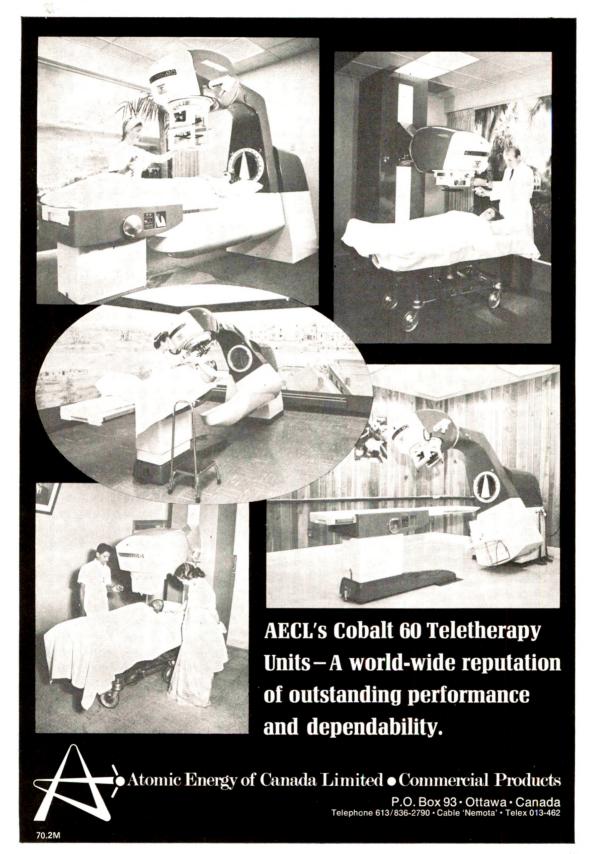
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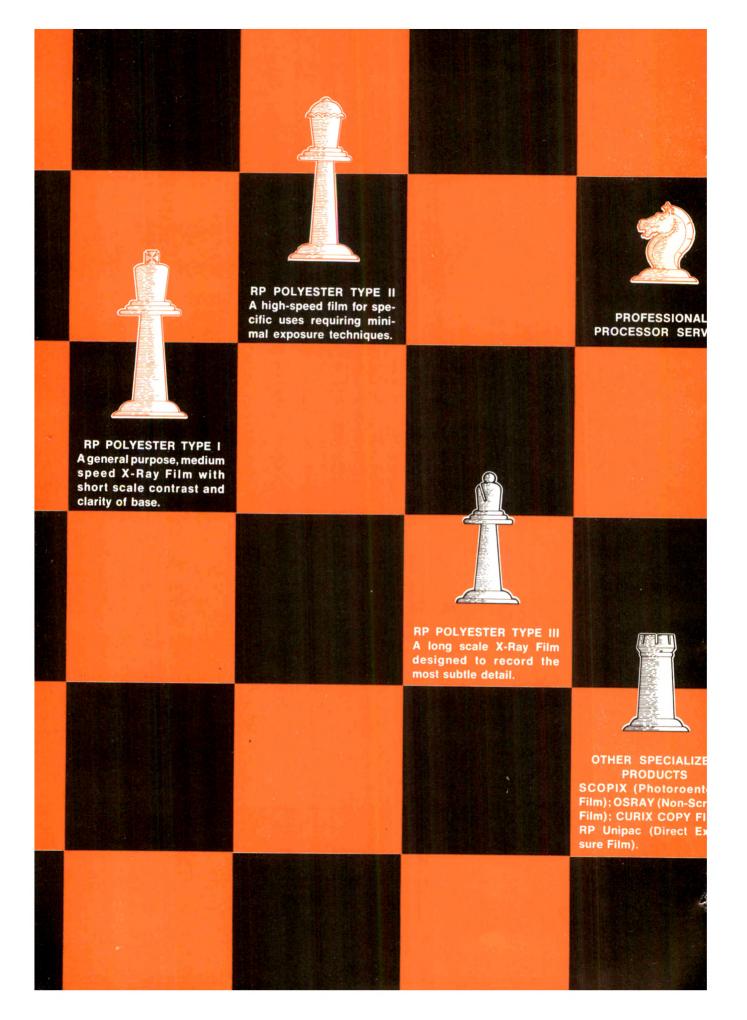
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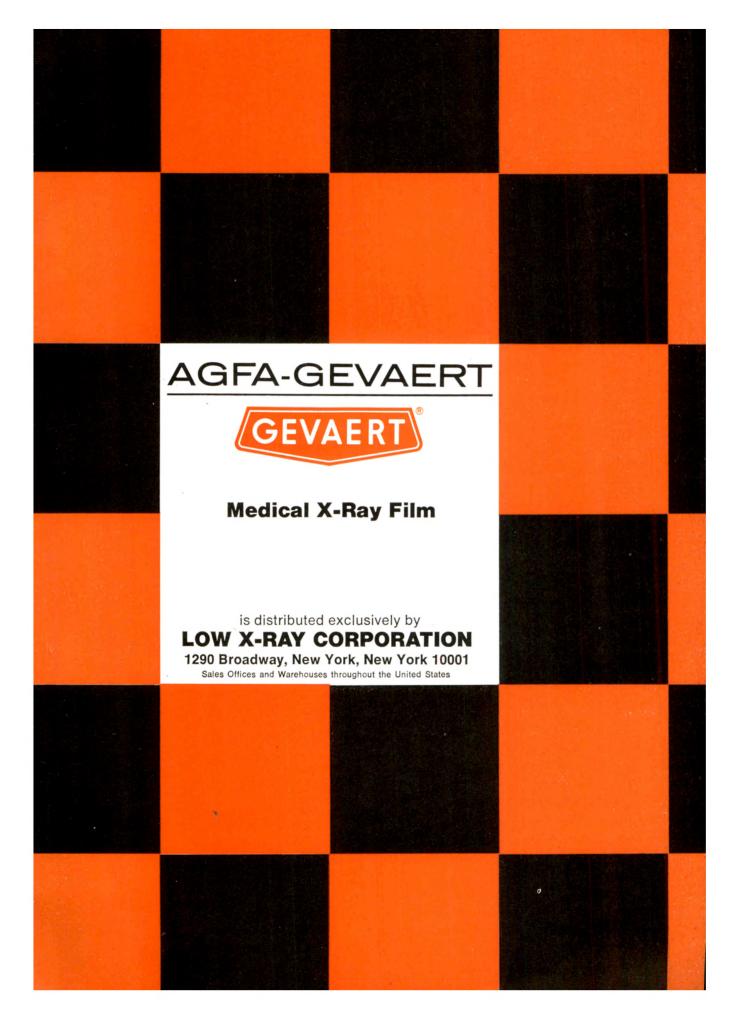
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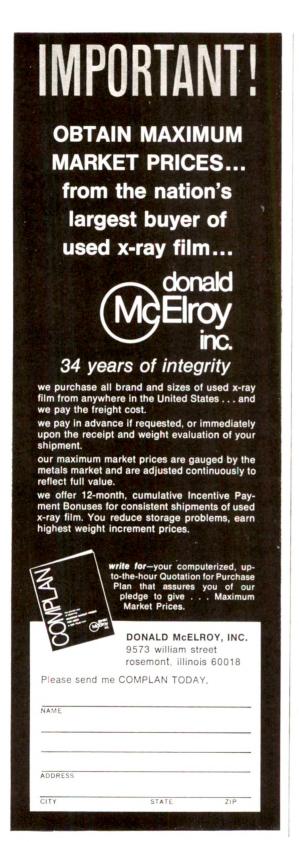
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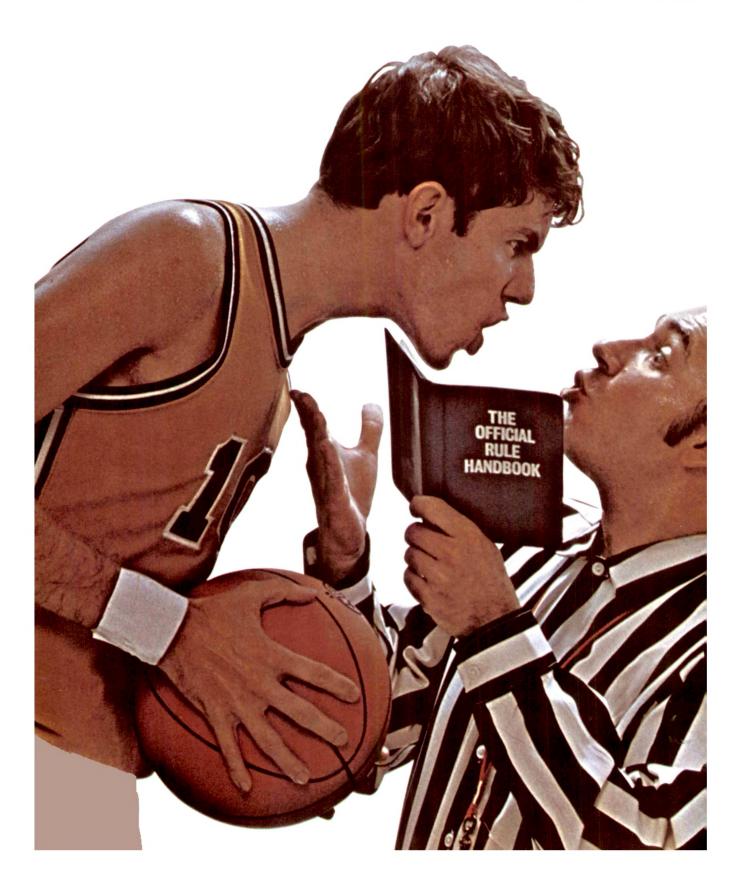
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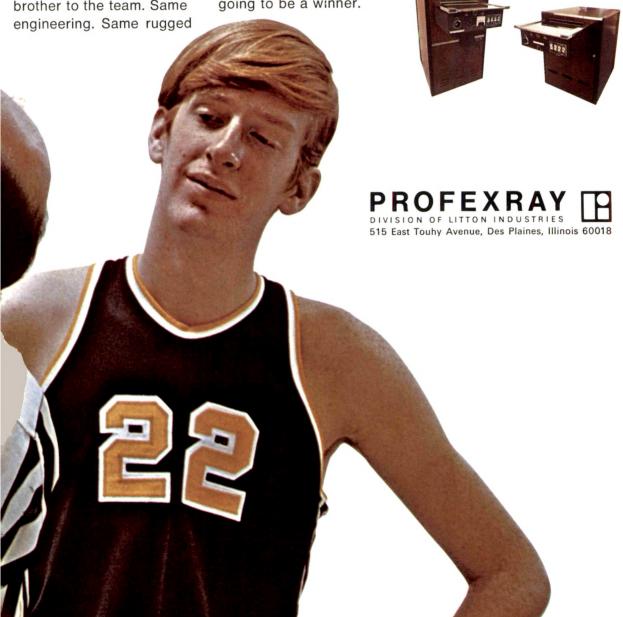
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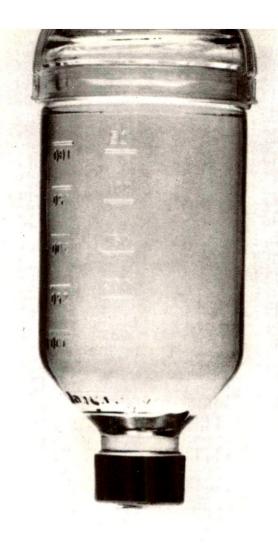
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Insert: Insert spike of infusion set into stopper of 300 ml. bottle.

#### Using sterile techniques and observing customary precautions



Infuse: Infuse into an antecubital vein over a period of 3 to 10 minutes



Discard: Discard entire unit when infusion is completed

#### **PRECAUTIONS**

PRECAUTIONS

Before a contrast medium is injected, the patient should be questioned for a history of allergy. Although a history of allergy may imply a greater than usual risk, it does not arbitrarily contraindicate the use of the medium. Premedication with antihistamines to avoid or minimize possible allergic reactions may be considered. Benadryle (brand of diphenhydramine hydrochloride) however, may cause precipitation when mixed with Hypaque sodium. The intravenous injection of 0.5 ml. to 1 ml. of the contrast medium approximately 15 minutes prior to infusion of the full dose is frequently used in an effort to detect patient sensitivity. The absence of a reaction to this test dose is not entirely reliable for predicting the patient's response to the full diagnostic dose. Severe reactions, including fatalities, have occurred with a test dose as well as with larger doses. Adequate facilities for treating severe reactions should be available.

Caution is advised in patients with severe cardiovascular disease and in

Caution is advised in patients with severe cardiovascular disease and in patients with a history of bronchial asthma or other allergic manifestations or of sensitivity to iodine.

or of sensitivity to iodine.

Contrast media have been shown to promote the phenomenon of sickling in individuals who are homozygous for sickle cell disease when the material is injected intravenously or intraarterially.

In myelomatosis, urography should only be performed with caution. If a weak protein-binding agent such as a diatrizoate is used for the procedure it is essential to omit preparatory dehydration, administer fluids, and attempt to alkalinize the urine.

It is essential to only preparatory delivation, delivation, to alkalinize the urine.

The results of PBI and RAI uptake studies, which depend on iodine estimations, will not reflect thyroid function for up to 16 days following administration of iodinated urographic media. However, function tests not depending on iodine estimations, e.g., T<sub>3</sub> resin uptake or direct thyroxine assays, are

not affected.

Immediate adverse reactions to drip infusion pyelography have not been reported to occur at a higher frequency or greater severity than with routine excretory urography. However, sequelae of this procedure are possible some hours after the examination. Drip infusion pyelography imposes not only a sudden osmotic load, but also may present as much as 160 meq. of sodium (3.7 Gm.) to patients with established, decreased glomerular filtration and renal tubular damage. In addition, these patients may also have coexisting or associated cardiovascular disease. Therefore, the possibility of the development of congestive heart failure hours after the procedure should be considered.

Because of the possibility of inducing temporary suppression of urine, it is wise to allow an interval of at least 48 hours to pass before repeating drip infusion pyelography in patients with unilateral or bilateral reduction of normal renal function

Preparatory dehydration or abdominal compression may not be pessessed

in infusion pyelography. In infants and young children and in azotemic patients, especially those with oliguria, dehydration is considered dangerous. ADVERSE REACTIONS

Reactions accompanying the use of contrast media may vary directly with the concentration of the substance, the amount used, the technique used, and the underlying pathology.

and the underlying pathology.

Adverse reactions, usually of a minor nature, have occurred in 10-14 per cent of patients who have received Hypaque intravenously. Reactions due to technique include hematomas and ecchymoses following extravasation from the vein, and pyrogenic reactions. Hemodynamic reactions include vasodilatation with flushing, hypotension and, rarely, vein cramp or thrombophlebitis. Serious cardiovascular reactions include rare cases of cardiac arrhythmias (e.g., ventricular fibrillation), shock, and cardiac arrest. Transient proteinuria may occur occasionally following the injection of radiopaques and, rarely, oliguria and anuria (renal shutdown) have been reported as a secondary effect of a hypotensive reaction. Allergic reactions include asthmatic attacks, nasal and conjunctival symptoms, dermal reactions such as urticaria and, rarely, anaphylactic shock, sometimes with fatal outcome. Severe reactions may also be manifested by signs and symptoms relating to the respiratory system (restlessness, confusion, or convulsions). Other reactions include nausea, vomiting, excessive salivation, anxiety, headache, and dizziness. Infrequently, "iodism" (salivary gland swelling) from organic compounds appears two days after exposure and subsides by the sixth day.

DOSAGE AND ADMINISTRATION

#### DOSAGE AND ADMINISTRATION

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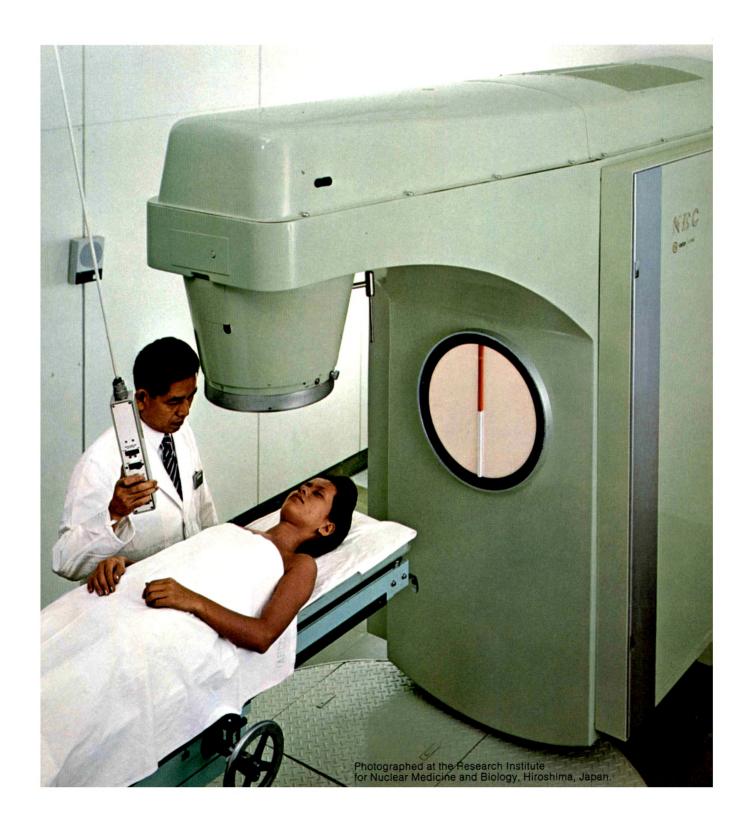
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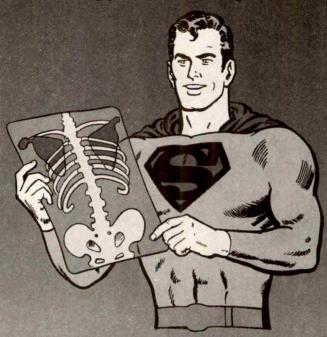
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"While X-Ray vision is instantaneous, Sakura's fast 90-second processing is certainly adequate," he injected, his vision piercing through the Sakura box and scanning the enclosed instructions. His eye focused on data indicating that Sakura 90-second film could also be hand processed as well as developed in a 7-minute or 3½-minute automatic processor. "Hmm," he reflected—obviously pleased with its versatility.

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#### NECROTIZING ANGIITIS ASSOCIATED WITH DRUG ABUSE\*

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RECENT angiographic observations have demonstrated that a necrotizing angiitis having the clinical and histopathologic characteristics of periarteritis nodosa is associated with drug abuse. This serious disease has not been previously recognized as a medical sequela of drug addiction. 4,11,16

#### CLASSIFICATION AND PATHOLOGY

Necrotizing angiitis is an appropriate collective term for several pathologic conditions characterized by a primary inflammation and necrosis of vessels.<sup>1,18,21,22,25</sup> The group includes: periarteritis nodosa, hypersensitivity angiitis, allergic granulomatous arteritis, rheumatic arteritis and the arteritis of collagen disease, temporal arteritis, and the arteriolar necrosis of malignant hypertension. The addition of the necrotizing angiitis of drug abuse into this classification is felt to be justified.

Pathologic and roentgenologic differential diagnosis involves periarteritis, hypersensitivity angiitis and arteriolar necrosis of hypertension. The lesions of periarteritis

are found most often in the kidney, pancreas, mesentery, gastrointestinal tract and muscles. They are rarely found in the spleen and pulmonary vessels but may involve the bronchial arteries. Usually the pathologic process begins as edema and acute inflammatory exudate in the intima of small and medium sized muscular arteries. Separation planes in the wall of the vessels may cause narrowing of the lumen. The destructive process has a predilection for vascular bifurcation sites, appearing in the hilar areas of the viscera and in the mesentery near its attachment to the intestine. Thrombosis and small aneurysms develop as a result of the acute inflammatory reaction that spreads through the wall of the vessel causing fragmentation of the internal elastic lamina. The vasculitis progresses to a chronic phase with granulation tissue and fibroblastic proliferation. The resulting lesions are collagenized scars; nodules are created in the wall of the vessel and obliteration of its lumen may result. Lesions produced in the gastrointestinal

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<sup>\*</sup> Presented at the Eighteenth Annual Meeting of the Association of University Radiologists, Lexington, Kentucky, April 29-May 1,



Fig. 1. Periarteritis nodosa. This 43 year old male was in good health until 6 months before his death. His illness was characterized by swelling of his legs, weakness, fever, synovitis of his knees, wrists and proximal interphalangeal joints, peripheral neuropathy and a weight loss of 52 pounds. A muscle biopsy demonstrated focal arteritis consistent with active periarteritis nodosa or rheumatoid arteritis.

Selective renal arteriogram, left kidney. Multiple microaneurysms (arrowheads) are present. The contour of the interlobar arteries is irregular and a diminution of number is apparent. The renal cortex is irregular.

tract may be infarcts of the liver, pancreas or intestine. Hemorrhage, ulceration and perforation of the intestinal wall can occur. 8,21 These pathologic features of necrotizing angiitis are discernible at the time of arteriography (Fig. 1). The histopathology and arteriographic features of drug abuse angiitis appear to be indistinguishable from periarteritis nodosa.

Hypersensitivity angiitis is an acute necrotizing inflammation which involves small arteries and often venules. The reaction is intense and frequently causes pneumonic foci. The spleen is commonly involved. It is most characteristic in the heart and lungs and, in contradistinction to periarteritis nodosa, it is rare in the intestine. The lesions of hypersensitivity vasculitis are all about the same age, whereas the coexistence of acute, chronic and healed lesions is a hallmark of periarteritis.

Inflammatory reaction is minimal or absent in the arteriolar necrosis of malignant hypertension. The necrosis is usually not considered to be fibrinoid in character and, as a result, some pathologists do not consider this process to be a primary vasculitis.<sup>21</sup> It is not difficult to distinguish from periarteritis associated with severe hypertensive renal disease.

#### CLINICAL SYNDROME

The clinical syndrome of drug abuse angiitis is strikingly similar to that of periarteritis nodosa with severe renal, gastrointestinal and cardiac involvement. The clinical manifestations depend upon the intensity of the reaction, the distribution and location of the lesions as well as the duration of the disease. The persistence of the etiologic agent in the body appears to bear on the progress of the disease. Pancreatitis, renal failure, pulmonary edema, peripheral neuropathy, arthralgias and myalgias have been common. The drug abuse patients have also shown a deterioration of visual acuity, apparently due to retinal angiitis. Hemolytic episodes that are not understood at this time have been noted. Fever, malaise, weakness and loss of weight reflect the systemic nature of the disease. Renal failure, hypertension, abdominal pain, liver dysfunction, appendicitis, pancreatitis, synovitis, and/or recurrent pulmonary edema have all been observed in the drug abuse patient.

#### MATERIAL AND METHOD

This angiographic study of medical complications of drug abuse involves 21 male and 9 female patients ranging from 19 to 56 years of age. The duration of drug use varied from 3 months to 20 years. Angio-

graphic studies were performed on patients presenting with clinical signs and symptoms of angiitis and some asymptomatic drug users chosen at random. As a control, other persons who had used heroin, cocaine or marihuana exclusively were studied. The usual patient had employed a wide spectrum of stimulants, narcotics, hallucinogens and depressants. Heroin and methamphetamine (methedrine), combinations of these, or combinations of methamphetamine and lysergic acid diethylamide (LSD) were used quite routinely. Methedrine is often employed to overcome drowsiness induced by heroin<sup>2</sup> and is also used as a heroin diluent. Barbiturates and strychnine may be taken to potentiate the effect of heroin. A typical drug history may also include oral and/or intravenous use of chlordiazepoxide HCl, diacetylmorphine, hashish, meperidine HCl, mescaline, oxycodone HCl, oxymorphone and "STP." Intravenous injections of extract of marihuana seeds, milk and wine have been recorded. Obviously, resolution of the problem of determining a specific etiologic agent or agents responsible for the vasculitis is extremely difficult. It is further complicated by the contamination of "street" and "homemade" drug preparations.

Bilateral selective renal arteriography is the first angiographic study performed in the investigation of the drug abuse patient, since the kidney appears to be the target organ of necrotizing angiitis. Following this, selective celiac and superior mesenteric arteriographies have been done routinely. However, when the intrarenal vascular pattern has been normal, vascular changes in other organs have not been demonstrated. Inferior mesenteric and bronchial arteriographies are reserved for special clinical situations.

In this series of 30 patients, angiography has provided positive evidence of necrotizing angiitis in 13 individuals. The diagnosis has been confirmed by postmortem histopathologic material in 3 patients. Ten of these 13 individuals admitted to the intravenous use of methamphetamine. The

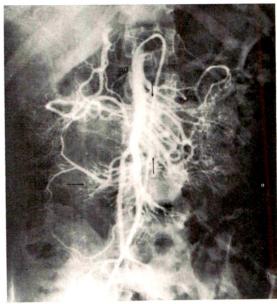


Fig. 2. Drug abuse angiitis. This 24 year old male gave a history of at least 125 LSD "trips" during a 2 to 3 year period of time. Selective renal arteriography showed equivocal changes; celiac arteriography was normal.

Superior mesenteric arteriogram. There is an unusual crowding of the jejunal and ileal branches toward the center of the abdomen. Most of the jejunal branches present stationary waves (vertical arrows). The distal jejunal and ileal branches are indistinct and irregular in contour (horizontal arrow).

daily use of intravenous methodrine over a 2 year period culminated in death from renal failure in one 19 year old boy. Two of the persons with positive angiograms were primarily heavy users of lysergic acid diethylamide (Fig. 2).

Equivocal angiographic findings have been noted in 8 persons (Fig. 3). In 2, it was not possible to determine whether the renal vascular changes indicated a primary angiitis or subacute glomerulonephritis. Nine persons had normal angiographic examinations. All of the patients who had employed only heroin, cocaine or marihuana were in this category.

#### ARTERIOGRAPHIC PATTERN OF ANGIITIS

The characteristic features of the vascular pattern of necrotizing angiitis are: (1)

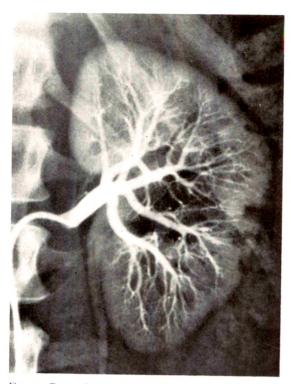


Fig. 3. Drug abuse angiitis. This 21 year old male was admitted to the hospital in a comatose condition. A recent history of seizures and the frequent use of intravenous methedrine was subsequently obtained. Carotid arteriography confirmed the clinical diagnosis of subarachnoid hemorrhage Scattered small emboli and an associated vasculitis were present.

Left selective renal arteriogram. Minimal vascular irregularity in the upper pole and midportion of the kidney is considered to be insufficient evidence for a definite angiographic diagnosis.

microaneurysms which show a predilection for bifurcation sites; (2) indistinctness of vessel outlines; (3) segmental luminal irregularities, *i.e.*, stenotic segments; and (4) obliteration and thrombosis of vessels (Fig. 4, A and B; 5, A–D; and 6, A–D).

The acute inflammatory reaction with edema and exudate in the intima of the vessel can cause significant narrowing of its lumen and indistinctness of its margins. As the process extends through the wall of the vessel and into the perivascular tissues, thrombosis can result and produce abrupt vessel terminations. Necrosis of the vessel wall with fragmentation of the internal elastic lamina permits microaneurysms to

form. They are most often seen in the hilar areas of abdominal organs, near the mesenteric attachments to the intestine and at bifurcation sites along the course of vessels. In most instances the aneurysms range from I to 5 mm. in diameter. They tend to retain contrast material during angiographic study so that their persistent opacification during the nephrographic phase or capillary-venous phase of hepatic or pancreatic arteriography simplifies their recognition (Fig. 5, A–D; and 6, A–D). Multiple radiolucent areas in the same angiographic phase is the appearance that is produced by the presence of focal areas of necrosis (Fig. 6, A-D). The mottled nephrogram of a kidney is frequently associated with scalloped irregularity of the renal outline. Involved kidneys usually show a diffuse glomerulitis so that cortical thinning and minimal changes of arteritis create a pattern similar to that of glomerulonephritis. Renal biopsy is necessary for differentiation of these two entities. The stage of chronic inflammation with granulation tissue progresses to that of collagenized scar formation in the vessel wall, which causes total obliteration of the vessel lumen. The affected tissue bed will show considerable sparsity of vessel branches and areas of tissue infarction. It is important to note that all stages, acute, chronic and healed, of the lesions of necrotizing angiitis are usually present simultaneously. While microaneurysms are the most characteristic arteriographic feature, advanced clinical disease may be present in the absence of visible aneurysms. The vascular pattern of periarteritis nodosa and the angiitis of drug abuse are indistinguishable roentgenographically.

Hypertension is a common feature of the clinical syndrome and not infrequently is the indication for angiographic study. Therefore, roentgenographic recognition of the vascular pattern of the arteriolar necrosis of malignant hypertension is important to differential diagnosis. When this arteritis is manifested only by sparsity of vessels, obliterations and scattered segmental ste-

noses of terminal arterial branches, the arteriographic pattern is very similar to certain stages of periarteritis. The diagnosis of this disease then requires clinical and biopsy confirmation or exclusion. Most often the intrarenal vascular pattern of malignant hypertension is distinguished by dilatation of the proximal renal artery divisions with a noticeable peripheral disproportion in luminal diameter (Fig. 7). In the advanced stage of malignant hypertension, isolated aneurysms occasionally involve the larger interlobar branches. They bear little resemblance to the multiple scattered microaneurysms or periarteritis.

The endarteritis obliterans and perivasculitis caused by chronic renal inflammatory disease may produce segmental narrowings of large interlobar arteries. The ectasia, tortuosity and course alterations that characterize chronic pyelonephritis are usually associated with parenchymal and pelvocalyceal changes that permit easy recognition of this type of vasculitis.

#### DISCUSSION

Periarteritis is an uncommon disease. The documentation that this clinical and pathologic syndrome has been definitely identified in 13 of 30 persons, each of whom

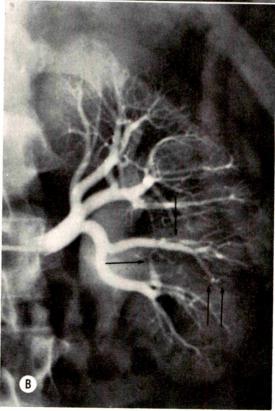
Fig. 4. Drug abuse angiitis. (A) This 20 year old female became obtunded when arrested for possession of dangerous drugs. There was a past history of seizures characterized by blackouts without aura. The patient had used intravenous methodrine for 2 to 3 years. A carotid arteriogram demonstrated scattered emboli and an associated vasculitis.

Right selective arteriogram. Minimal but definite vascular changes of sparsity, luminal irregularity and small vessel obliteration are seen in the midlateral portion and medial aspect of the lower pole of the kidney.

(B) This 21 year old male frequently used oral and intravenous methodrine.

Left selective renal arteriogram. There are early changes of necrotizing angiitis. Single arrows desig-





nate luminal irregularities. Double arrows point to small microaneurysms.

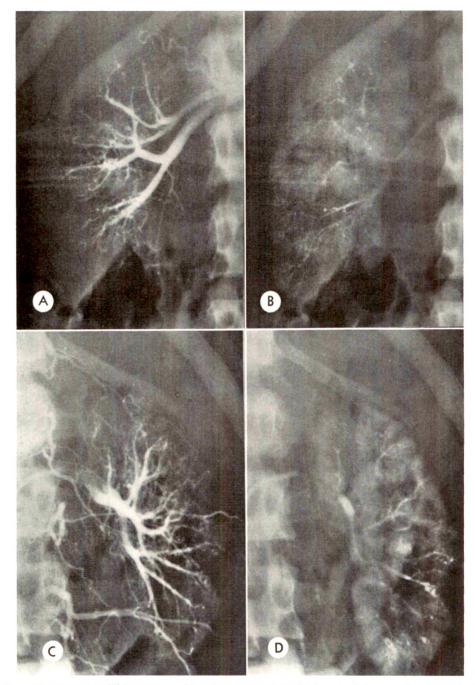


Fig. 5. Drug abuse angiitis. This 19 year old male presented multiple complaints at the time of admission: urinary frequency, vomiting, headache, diminished vision in his left eye and generalized tremors that had been present for 2 days. Methedrine abuse consisted of daily intravenous injections for 2 years. Blood pressure was 195/135 mm. Hg; visual acuity—left eye 20/120 with blurred disk margins, right eye 20/40. Papilledema, bilateral retinal detachments and encephalopathy developed. There was progressive deterioration of renal function and the patient's course was unaffected by all therapy. Death occurred 1 month after the onset of illness.

Selective renal arteriograms. (A and B) Right. (C and D) Left. A severe necrotizing vasculitis is present; the intrarenal vessels are indistinct; there are irregular stenoses, arterial thromboses and multiple scattered microaneurysms. The renal cortex is thinned and irregular.

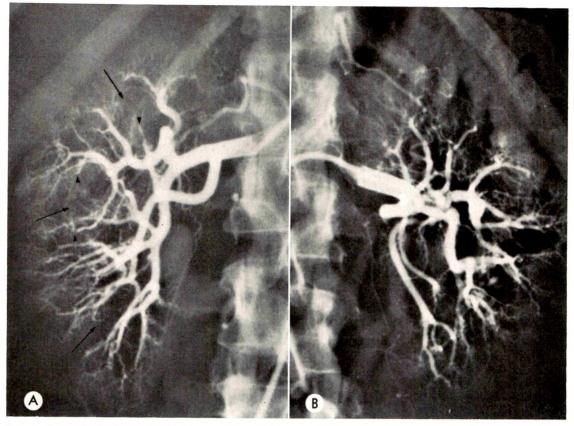


Fig. 6. Drug abuse angiitis. This 32 year old female was a chronic alcoholic and known heroin addict who admitted to the use of other intravenous drugs including methodrine. She had had prior treatment for pancreatitis and gastrointestinal bleeding and now presented with a chief complaint of constant epigastric pain. There had been recent fever, weight loss and nonproductive cough. Her course was downhill. There were fever spikes to 103°F.; persistent abdominal tenderness, cardiomegaly and many episodes of pulmonary edema, marked muscle wasting, weight loss to 65 pounds and mild hypertension. The patient died 6 months after hospitalization.

Selective renal arteriograms. (A) Right. (B) Left. Arrowheads show thrombotic vessels. Arrows point to avascular radiolucent areas of focal necrosis. The renal cortex is thin and irregular. In A there are also a few small microaneurysms.

presented a history of flagrant drug abuse, leads to the inescapable inference that one or more of the commonly used drugs is a specific cause of necrotizing angiitis. To what extent our understanding of the morbidity and mortality in drug addicts has been enhanced remains to be proved.

The radiologic literature contains only a few discussions of some of the medical complications of drug use.<sup>17,24</sup> These reports have been concerned with pulmonary manifestations of bronchopneumonia, septic pulmonary emboli and pulmonary edema due to intravenous injections of drugs by

addicts. The angiographic characteristics of periarteritis have been cited in several reports<sup>5,7,9,10,12,14,15</sup> and the roentgenographic features of perirenal hematoma as a complication of the angiitis have been reviewed. <sup>13,20</sup> Only a single report of involvement of the digestive system represented by a case of ulcerating jejunitis was found in the literature. <sup>8</sup> Ocular manifestations of necrotizing angiitis are uncommon but iritis and retinal vasculitis in this disease have progressed to occlusion of the central retinal artery and produced blindness. <sup>19</sup> Diminished visual acuity occurred in 2 pa-

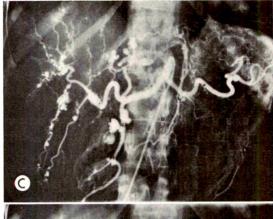




Fig. 6. Selective celiac arteriograms. (C) Arterial phase. Many aneurysms involve the intrahepatic arteries, the bifurcation sites of the gastroduodenal artery (G), the left gastric artery (L), the dorsal pancreatic artery (D), and the pancreatic rami of the splenic artery (P). (D) Capillary-venous phase. There is a dramatic persistence of contrast material in many of the aneurysms.

tients in the drug group. Ophthalmologic examination revealed a frank retinal angiitis in I patient whose presenting complaint was severe visual problems. Recently, instances of spontaneous subarachnoid hemorrhage have occurred incident to methedrine use. Carotid arteriography in these cases has revealed the presence of disseminated small emboli with an associated vasculitis.23 These findings were present in 2 individuals of this series. Postmortem examination of I patient demonstrated scattered areas of infarction of the pons secondary to necrotizing angiitis. It is possible then that organic brain lesions may, in part, explain some of the mental aberrations, bizarre behavior responses and adverse reactions sometimes caused by psychotrophic drugs.

The wide variety of drugs taken orally and intravenously by the drug abuse patient, the contamination of the drugs used and the lack of purity of the preparations make the recognition of the causative agent of the drug abuse syndrome extremely difficult. Reproduction of the pathologic process in a laboratory animal will be required. At this time, circumstantial evidence tends to indict methamphetamine.

#### SUMMARY

Angiography has revealed a high incidence of the clinical and pathologic syndrome of necrotizing angiitis in drug abusers. Positive evidence supported by 3 postmortem reports has been uncovered in 13 of 30 patients. Eight additional patients

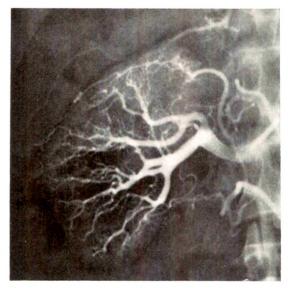


Fig. 7. Arteriolar necrosis of hypertension. This 38 year old male was hospitalized for renal failure and hypertension (blood pressure 210/130 mm. Hg). Grade IV eyeground changes were present; blood urea nitrogen was 60 mg. per cent. His underlying disease was considered to be chronic glomerulonephritis.

Right selective renal arteriogram. The intrarenal vascular pattern shows pruning, coiling, luminal irregularities, peripheral attenuation of the vessels with considerable disproportion between the secondary and tertiary divisions. The capsular vessels are prominent. had angiographic changes of an equivocal nature.

Angiitis of drug abuse has been added to the classification of necrotizing angiitis.

The clinical and pathologic features of periarteritis nodosa and the angiographic patterns of necrotizing angiitis are presented.

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#### CEREBRAL ARTERIAL DISEASE IN CHILDREN\*

AN ANGIOGRAPHIC STUDY OF 40 CASES

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THERE is, as yet, no satisfactory explanation as to the etiology and pathogenesis of sudden hemiplegia in children—the "pediatric stroke." The clinical details of the syndrome have been reported in detail. There has been, however, no satisfactory concomitant study of the angiographic appearance of the cerebral arterial lesions occurring in many of these children.

The purpose of this study is to describe the cerebral arterial lesions as seen with angiography in 40 children. These children had no other lesions to which their sudden hemiplegia could be ascribed. It is intended that this angiographic study will both complement the comprehensive clinical reports and provide a simple but practical classification of the sites of the arterial lesions. The relationship between: (a) angiographically detected irregularities of the internal carotid artery in the neck and intracerebral arterial disease; and (b) a history of nasopharyngeal infections and such arterial irregularities will be demonstrated.

In our experience, it is the angiographic appearance of the arterial lesion that alone provides the basis for any etiologic theory. There is a paucity of pathologic data concerning these lesions in that they are rarely surgically exposed and are not fatal.

#### MATERIAL

During the period from 1953 to 1970, 175 children, having been previously normal, presented at the Hospital For Sick Children, Toronto with an acute onset of a pro-

found hemiplegia. No antecedent or other concurrent neurologic or cardiovascular abnormality was present in any of these children. This excluded a possible relationship between the hemiplegia and a head injury, intracranial space occupying lesion or infection, arterial venous malformation, congenital or acquired cardiac disease, hematologic disorder, endocrine abnormality, intoxication or Todd's paralysis. A hemiplegia ascribed to the birth process was similarly excluded. No abnormal cholesterol values were present in those children on whom this test was performed.

We considered it valid to include 4 children with intraoral trauma and subsequent hemiplegia. The known etiologic agent, a sharp object, produced an arteritis of the internal carotid artery with a similar distal angiographic picture to those arterial lesions without such a known external cause. Sixty per cent of the remaining 36 children had a pharyngitis or tonsillitis, a high fever or a childhood exanthema during the few months prior to the onset of the acute hemiplegia. A number of children also had an ill-defined period of being vaguely unwell prior to this onset. Four children, having been quite well immediately before the hemiplegia, developed an associated hyperpyrexia which abated within 12 hours, and I child experienced a fever of 106°F. for a brief period. Six children complained of a poorly localized abdominal discomfort. Two children were hypertensive and one will be considered in detail. Six children were performing strenuous exercise at the time of onset of the

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hemiplegia. Associated convulsions occurred in only 4 patients and all were minor and temporary, the most prolonged seizure occurred in a child with multiple peripheral middle cerebral occlusions.

Cerebral angiography was performed on 61 children, 40 of whom had one or more abnormalities of the internal carotid artery or vertebral artery and their intracranial branches. The angiographic appearance of the cerebral vascular abnormalities in these 40 children forms the basis of this report.

#### RESULTS

#### I. AGE AND SEX

The 22 girls slightly outnumbered the 18 boys, and the 40 children varied in age from 1 to 14 years (Fig. 1). Two peak age groups occurred between 1 and 3 and between 6 and 11 years. The relationship between the age of the child and the site of the arterial lesion will be described later.

#### 2. SITE OF THE ARTERIAL ABNORMALITIES

There was a total of 73 lesions in the 40 children. The majority occurred in the supraclinoid portion of the internal carotid artery (24), and in the proximal middle cerebral artery (20) (Fig. 2). The anterior cerebral and the distal middle cerebral arteries were each involved in 10 children, the extracranial internal carotid in 7, and the vertebral and the basilar each involved in 1 child.

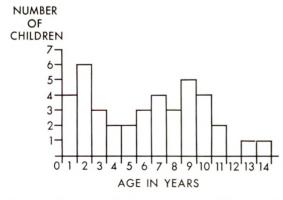


Fig. 1. The age distribution of 40 children with cerebral arterial lesions.

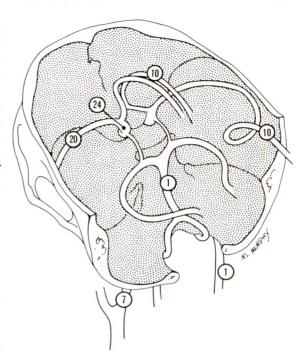


Fig. 2. Sites of the 73 arterial lesions in 40 children.

#### 3. CLASSIFICATION OF THE CEREBRAL ARTERIAL LESIONS

This classification is based on the sites of the arterial irregularities or occlusions (Table 1). These occurred either in the extracranial portions of the internal carotid (Group 1) or the intracranial arteries, and, if intracranial, the lesions were either unilateral or bilateral.

The unilateral intracranial arterial le-

Table I

CLASSIFICATION OF CEREBRAL ARTERIAL

LESIONS IN CHILDREN

Group I	Extracranial internal carotid or
	vertebral arterial lesions 5
	Internal carotid 4
	Vertebral I
Group II	Unilateral intracranial arterial lesions 31
	(a)Internal carotid 15
	complete 5
	incomplete 10
	(b) Middle cerebral only 16
	proximal 11
	distal 5
Group III	Bilateral intracranial arterial lesions 4

sions (Group II) were divided into 2 subgroups. In the first, the internal carotid artery was involved either as a complete obstruction, or if the obstruction was incomplete, additional distal lesions were always present in the middle cerebral artery, the anterior cerebral artery, or both. A second subgroup of unilateral intracranial arterial lesions consisted of those involving the proximal or distal middle cerebral artery, without internal carotid artery involvement. (The proximal portion of the middle cerebral artery is that part from its origin to its trifurcation.)

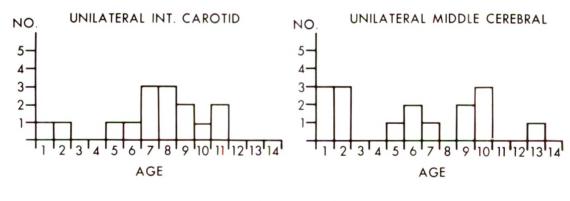
Children with bilateral intracranial arterial involvement formed Group III. The term bilateral is preferred to multiple as the angiographic appearance of bilateral arterial disease (although indeed multiple) is distinctly different from multiple unilateral arterial disease. This bilateral group included children with a compromise of the circle of Willis at more than one site; *i.e.*, in both carotid arteries, or in one carotid together with the basilar artery.

The majority of children (78 per cent) had unilateral intracranial arterial lesions. Approximately one-half of these lesions involved the internal carotid artery (with or without distal involvement) and the other half involved the middle cerebral artery only.

The pattern of the ages of the children in each group revealed a preponderance of children between the ages of 6 and 11 years in the unilateral internal carotid subgroup (Fig. 3), whereas a distinct separation of children occurred in the unilateral middle cerebral subgroup into those of 1 to 2 and those of 6 to 10 years of age. Children in Group III were all under the age of 5 years.

Group I—Extracranial Internal Carotid or Vertebral Arterial Disease.

The internal carotid artery was completely obstructed in 4 of the 5 children and this obstruction resulted from direct intraoral trauma with a sharp object. Subsequent angiography demonstrated a characteristic irregular tail-like obstruction of



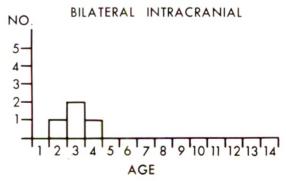


Fig. 3. Age distribution in Groups II and III.

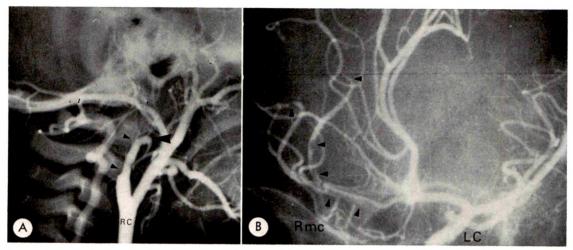


Fig. 4. (A) Irregular tail-like obstruction of the right internal carotid artery. (B) Cross-filling of right middle cerebral artery from a left carotid angiogram in an oblique view. Note beaded emboli in the proximal and distal middle cerebral artery. RC=right carotid artery. Rmc=right middle cerebral artery. LC=left carotid artery.

the internal carotid artery in 3 children, and filling of the supraclinoid portion of the same internal carotid artery by collaterals via the ophthalmic artery. In the fourth child, however, a contralateral internal carotid angiogram with a fortuitous crossfilling, revealed numerous discrete intraluminal middle cerebral emboli on the traumatized side (Fig. 4, A and B). These cases are included in this study in order to develop the concept of a cervical carotid arteritis occurring in children with a sudden hemiplegia.

An occlusion of the vertebral artery (Fig. 5, A, B and C) in the fifth child was clinically quite spontaneous, and angiography prompted by a basilar artery syndrome revealed also a distal basilar artery occlusion.

Three additional children were found to have a discrete stenosis of the extracranial internal carotid artery varying from 1 to 3 cm. in length. Two had associated supraclinoid occlusions of the same internal carotid artery and another had an ipsilateral middle cerebral artery lesion. All had had a severe upper respiratory tract infection within 6 weeks prior to the hemiplegia. As there was also a significant intracranial arterial lesion in each child, we placed these 3 children in Group II.

Group II—Unilateral Intracranial Arterial Disease.

(a) Internal Carotid Artery. The majority of the 15 children in this subgroup were between the ages of 6 to 11 years, and there were 9 girls and 6 boys.

In the 5 children with a complete occlusion of the internal carotid artery, the site of occlusion was just distal to the ophthalmic artery in 2 (Fig. 6) and distal to the anterior choroidal artery in 3.

Ten children had an incomplete occlusion of the supraclinoid portion of the internal carotid artery and in *all* these children there was one or more associated distal arterial lesions (Fig. 7). Two of the 10 children had associated stenotic lesions of the extracranial internal carotid artery (Fig. 8, A and B) and both had had a recent nasopharyngeal infection.

There was a considerable variation of the angiographic appearance of lesions involving the wall of the supraclinoid portion of the internal carotid artery. The web-like projections into the arterial lumen (Fig. 9), the dilated erect configuration of the supraclinoid portion (Fig. 10) and a discrete stenotic lesion of the internal carotid artery (Fig. 11, A and B) were particularly striking. The partial occlusion of an anterior cerebral artery with an associated internal

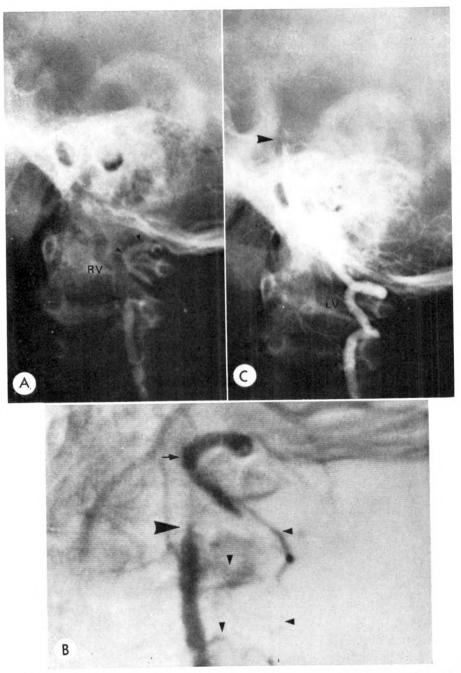


Fig. 5. (A) An occlusion of the right vertebral artery, with (B) numerous local collaterals and (C) a distal basilar obstruction. RV=right vertebral artery. LV=left vertebral artery.

carotid lesion and middle cerebral obstruction was clearly due to a distal thrombus (Fig. 12).

(b) Middle Cerebral Artery. Sixteen children had middle cerebral arterial lesions, 4

of whom had associated anterior cerebral artery involvement. There were 12 females in this subgroup, and 6 of the 16 children were under the age of 2 years (compared with only 2 of the 15 children with internal

carotid involvement). All the 6 children under 2 years of age were female. Eleven children had involvement of the proximal middle cerebral artery and the lesions were either occlusive (Fig. 13, A and B) or had nonocclusive irregularities of the wall of varying lengths. One child revealed a remarkable beaded appearance of the middle cerebral artery (Fig. 14A) which had a striking resemblance to that in a child reported by Bickerstaff.3 The child in our series had had a severe nasopharyngeal infection 4 weeks prior to the onset of the hemiplegia. The internal carotid artery, at that time, had a normal angiographic appearance. Three years later a repeat angiogram demonstrated a slightly less irregular middle cerebral artery and, in addition, a discrete stenosis of the cervical portion of the internal carotid artery on the same side was present (Fig. 14, B and C). We consider this latter stenosis evidence of an arterial lesion, probably a sequel to an arteritis of that portion of the artery due to the nasopharyngeal infection. The original

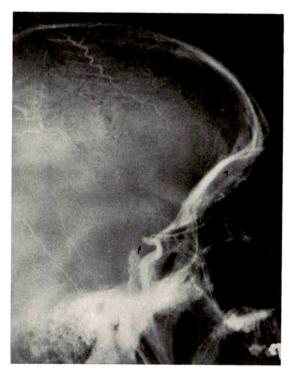


Fig. 6. A complete obstruction of the internal carotid artery distal to the ophthalmic artery.

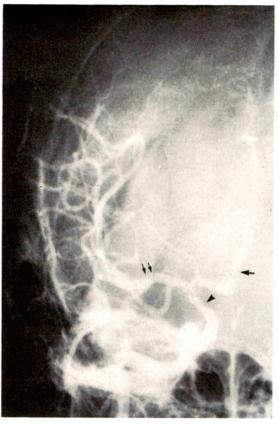


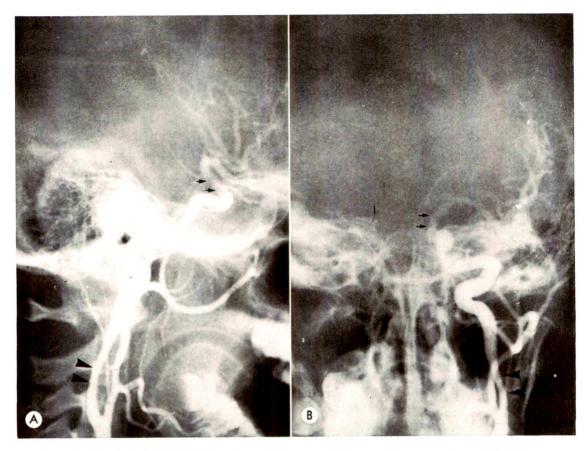
Fig. 7. Stenosis of the internal carotid artery and distal lesions in the anterior and middle cerebral afteries.

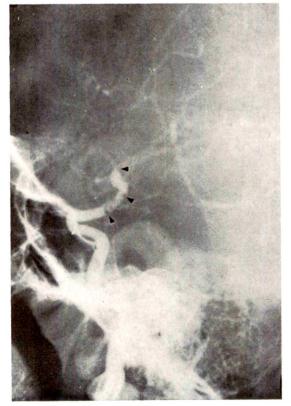
appearance of the middle cerebral artery was not that of emboli but rather of an abnormality of the arterial wall.

Occlusive disease in the distal middle cerebral artery only occurred in 5 children, and had the appearance of multiple emboli in the peripheral vessels. These children had no evidence of a proximal source of emboli, but 2 of the 4 children had had a recent nasopharyngeal infection. The angiographic appearance of the internal carotid arteries was normal in all 4 children.

Group III—Bilateral Intracranial Arterial Disease.

All the 4 children in this group were under 5 years of age and 3 were boys. A boy and a girl were siblings and a sister in the same family has an as yet uninvestigated hemiplegia. None was a Japanese.





All these children showed the characteristic mass of tortuous deep cerebral collaterals that have been described in the Japanese literature<sup>4</sup> and previously but erroneously thought to be confined to that race.

A remarkable demonstration of the angiographic appearance of the lesions in this group occurred in a 4 year old boy who entered our hospital for a tonsillectomy. He was otherwise well. He developed a sudden right hemiplegia in the immediate post-operative period and total cerebral angiography demonstrated bilateral intracranial internal carotid artery occlusions, distal to the ophthalmic artery on the right and distal to the anterior choroidal artery on the

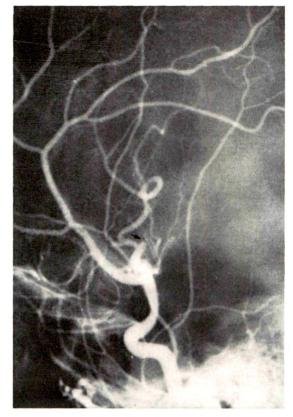
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Fig. 9. Web-like defects in the lumen of the internal carotid artery.

Fig. 8. (A and B) An irregular supraclinoid internal carotid artery with occlusion of the proximal anterior cerebral and distal middle cerebral arteries. Note the marked narrowing of the proximal cervical internal carotid artery and its dilatation before entering the head.



left (Fig. 15, A and B). The basilar artery was patent but the right posterior cerebral artery did not fill and probably arose from the occluded right internal carotid. Central collateral vessels were visualized at that time (Fig. 15C). Four months later, repeat angiography demonstrated an increased



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Fig. 10. Dilatation and straightening of the supraclinoid portion of the internal carotid artery with distal middle cerebral artery obstruction.

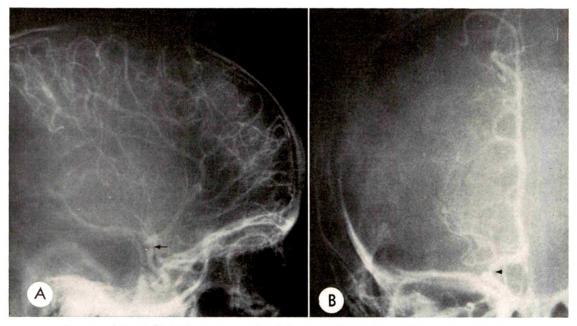


Fig. 11. ( $\mathcal{A}$  and  $\mathcal{B}$ ) A discrete stenosis of the supraclinoid, internal carotid artery and obstruction at the origin of the middle cerebral artery.

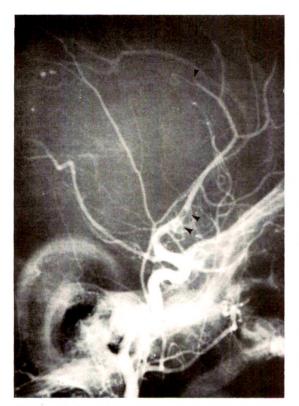


Fig. 12. A thrombus partially obstructing the proximal anterior cerebral artery and a distal occlusion in the same artery.

number of profuse central collaterals which arose from the posterior communicating and posterior cerebral arteries (Fig. 15D). As he also had a moderate hypertension, selective renal angiography was performed and there was an irregular stenotic lesion of the right renal artery (Fig. 15E). We have concluded that the tonsillectomy had an added effect to a pre-existing general arterial disease of unknown origin involving both the cerebral vessels and the renal artery. The aorta appeared normal, as did the abdominal vessels. The patient died subsequent to a progressive hypertension, cardiac failure and pneumonia, and permission for an autopsy was refused.

A 3 year old boy had a sudden right hemiplegia after a 12 month history of weight loss and listlessness, but with no evidence of a specific disease. A right carotid angiogram showed a virtual complete occlusion at the bifurcation of that internal

carotid and irregularity of the proximal middle cerebral artery (Fig. 16A). Large collaterals arose from the anterior choroidal artery which continued into the posterior choroidal vasculature on that side. Many additional small deep collaterals arose from the posterior cerebral artery. Twelve years later, total cerebral angiography demonstrated the right-sided lesion to be relatively unchanged, a partial occlusion of the distal internal carotid (Fig. 16B) and stenoses at the origins of the anterior cerebral and middle cerebral arteries on the left side with profuse local collaterals around these stenoses. A vertebral angiogram (Fig. 16C) showed large tortuous collaterals which arose from the tip of the basilar artery and passed centrally and anteriorly to feed the proximal right middle cerebral artery. Large collaterals from the left posterior cerebral artery passed centrally together with large posterior choroidal arteries and a dilated posterior callosal artery fed the distal anterior cerebral arte-

All these cases demonstrated a basic abnormality, which was disruption of the circle of Willis at 2 sites with inadequate collateral circulation through the circle itself. The development of large and profuse central cerebral collaterals followed.

Another child with such collaterals and an occlusion of one internal carotid artery distal to the posterior communicating artery (Fig. 17) did not have total angiography initially. This child has been placed in Group II as one with unilateral disease. The carotid angiogram, however, demonstrated reflux of contrast medium into the basilar artery and it appeared that a block of the basilar artery may indeed have been present. No vertebral angiography was performed. One may presume that this case could be placed in Group III and a stenosis of the other carotid artery may also be present, as these profuse central collaterals do not occur in unilateral arterial lesions.

A child, not included in this series, had a proven frontal astrocytoma. She developed a hemiplegia after a course of radiation

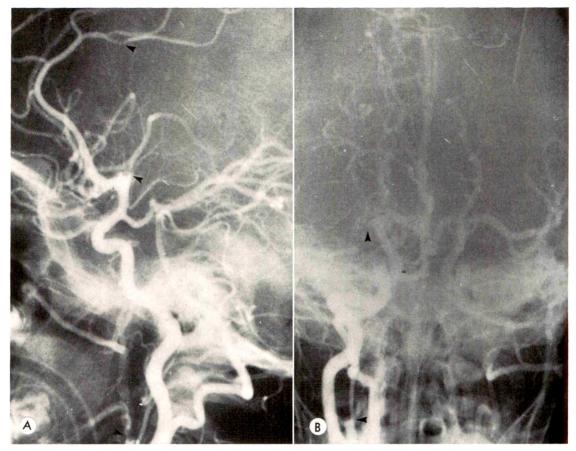


Fig. 13. (A and B) Complete occlusion of the proximal middle cerebral artery.

therapy to the head. Angiography demonstrated an occlusion of both the supraclinoid portion of the internal carotid artery and the tip of the basilar artery. This child, too, had profuse central collaterals with arterial occlusions due to an acquired radiation arteritis.

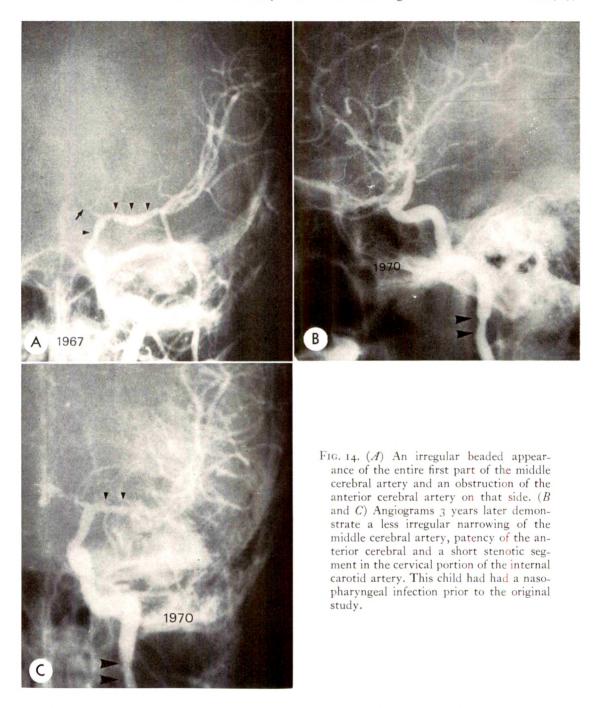
In our experience the cases that we have included in Group III have not shown progressive occlusions, but rather have developed progressive central collaterals.

#### DISCUSSION

The syndrome of acute hemiplegia in children rarely results in death. The angiographic demonstration of the lesions in the cerebral arteries that occur in some of these children provides the only objective evidence of the etiology of such a hemiplegia. A few children have had these lesions sur-

gically exposed and repaired<sup>6</sup> but the results have been unrewarding. The pathologic specimens obtained from these children and from the affected arteries in the few autopsy studies have provided evidence of both thrombi and mural changes, presumed to be sequelae of an inflammatory process. Both Bickerstaff<sup>3</sup> and later Shillito<sup>6</sup> were convinced that there is a direct relationship between nasopharyngeal infections and subsequent acute hemiplegia in some children. We support this concept.

In our study of 40 children, each with an acute hemiplegia, we found that the sites of involvement of the arterial lesions could be classified into the 3 groups described in this report. This study was, in most part, retrospective. Consideration of Group II suggests that angiographic evidence of a cervical internal carotid lesion is rare but,



when present, is the primary site of the arterial disease. The distal involvement that occurred in all of these cases was presumed to be one or both of two sequelae. It was either due to resultant emboli with subsequent thrombosis and reactive changes in the wall of the vessel distally, or

due to extension of the arteritis to the supraclinoid portion of the internal carotid artery and/or its branches. Evidence of distal emboli from a proximal arteritis is best exemplified by the findings demonstrated in Figure 4, an arteritis known to be caused by trauma. Similar findings oc-

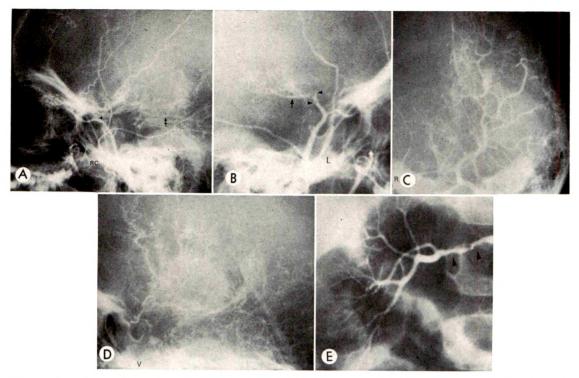


Fig. 15. A 4 year old boy with bilateral intracranial internal carotid artery occlusions. (A) Distal to the ophthalmic artery on the right with central collaterals and rete mirabile from the anterior meningeal artery, and (B) distal to the anterior choroidal artery on the left. (C) A few central collaterals arose from the left posterior cerebral artery. The right posterior cerebral artery did not fill. (D) Four months later a selective vertebral angiogram demonstrated a progressive development of the deep central collaterals. (E) A long irregular stenosis of the right renal artery was also present. RC=right carotid artery. L=left. R=right. V=vertebral.

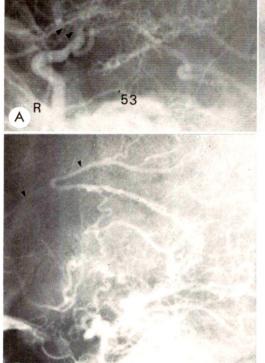
curred in a child that had a history of respiratory tract infection (Fig. 8, A and B; and 14, A, B and C) and in a child with an idiopathic vertebral artery occlusion and a distal basilar block (Fig. 5, A and B). It is our intention in the future to classify the children that have demonstrable arterial lesions in both the neck and the head in Group 1 and Group 11 (a) or (b), rather than in the latter subgroups alone.

The slight preponderance of females in our group of children is similar to that in previous reports. Of the 10 children that were 2 years of age or under, 8 were female. The preponderance of females was particularly marked in Group II (a) and (b), whereas 3 of the 4 children in Group III were boys.

The age distribution of the children was particularly interesting and suggested that if a child with an acute hemiplegia was 2 years or less and female, a lesion of the middle cerebral artery only was likely. Few children were between the ages of 2 and 6 years, whereas the majority of children in the 2 larger groups, Group II (a) and (b), were between the ages of 6 and 11 years.

The site of involvement had little effect on the course of the hemiplegia. Only 2 of the 40 children regained virtual full function of their limbs on the affected side. An alternating hemiplegia occurred in 2 of the 4 children in Group III. No specific clinical sequel was characteristic of any group.

In the group of 21 children who had a sudden hemiplegia with a normal arteriogram, the frequency of associated severe and prolonged convulsions was high (20 per cent). These were not encountered in the group with demonstrable arterial lesions.



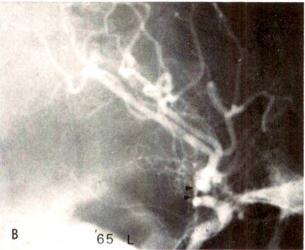


Fig. 16. (A) Partial occlusion of the distal right internal carotid artery with large central and choroidal collaterals. (B) Twelve years later a discrete stenosis of the left internal carotid artery with local collaterals is demonstrated. (C) A vertebral angiogram demonstrates large collateral vessels from the tip of the basilar artery itself, the enlarged posterior choroidal vessels and a dilated posterior callosal artery feeding the distal anterior cerebral artery. R = right. L = left.

This finding is in agreement with that reported by Aircardi *et al.*<sup>1</sup> Some of the normal angiographic studies were performed within 2 hours after the onset of the hemiplegia and, in particular, angiograms in 7 children with acute migrainous hemiplegia were all normal.

The association of a recent history of a nasopharyngeal infection and the onset of an acute hemiplegia in this study and in some smaller series,<sup>3,6</sup> is most significant. We have noted that there is a similar association with a recent history of an exanthema or a high fever due to varying causes, or an immediate association of strenuous exercise and the onset of the hemiplegia. Of the 2 children who had an associated

hypertension, only in I child was it severe and persistent and in this child there was an extensive renal artery stenosis and occlusion of the external carotid artery on one side, in addition to bilateral intracranial arterial occlusions. This child clearly had pre-existing arterial disease, as angiography revealed extensive deep collaterals at the onset of the acute hemiplegia, which occurred immediately after tonsillectomy.

The renal artery lesion in the I child in Group III has a distinct angiographic resemblance to arterial fibromuscular dysplasia. Were the lesions in his intracranial carotid arteries similar or were they due to emboli from a previously undetected bilateral arteritis in the neck? Fibromuscular

dysplasia has yet to be reported in the intracranial arteries. Two of the children in Group III were siblings, a factor that suggests a common underlying undue arterial sensitivity.

Tortuosity and kinking of the cervical internal carotid artery is reported to be associated with a hemiplegia on that side.<sup>5</sup> In our personal experience of over 800 angiograms of the cervical and intracranial vessels during the past 3 years, we have demonstrated marked kinking of the internal carotid artery in 20 children, none of whom had an associated acute hemiplegia. A discrete stenosis of the cervical portion of the internal carotid artery has not been seen other than those described in this report.

We consider it reasonable to suggest, in the light of our experience, that a local nasopharyngeal infection or a marked systemic illness with a high fever in some children results in an arteritis of the internal carotid artery, either in the neck or intracranially or both. We also suggest that, in some children, this arteritis may extend to or even primarily involve the middle cerebral artery. There may be an underlying but latent arteritis prior to the infection, or the cranial arteries may be particularly sensitive at some sites to the local or systemic effects of infections, exercise or unexplained fever.

#### SUMMARY

Sixty-one of 176 children under the age of 14 years, who suffered an acute hemiplegia, underwent angiographic studies of the cranial vessels. This hemiplegia was not related to any intracranial mass lesion, infection, cardiac or hematologic abnormality. One or more lesions of the internal carotid artery and its branches or the vertebrobasilar system were demonstrated in 40 of these children.

The sites of these lesions have been classified into 3 groups:

Group I—Extracranial internal carot-

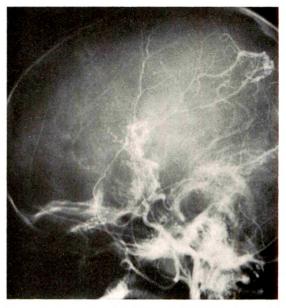


Fig. 17. An occlusion of the right internal carotid artery with profuse central collaterals from the artery itself. Note a presumed block of the distal basilar artery.

id or vertebral arterial disease

Group II—Unilateral intracranial arterial disease

(a)Internal carotid artery (complete or incomplete)

(b) Middle cerebral artery only

Group III-Bilateral intracranial arterial disease.

There was a distinct relationship between a history of a recent nasopharyngeal infection, exanthema, high fever, or severe exertion and the development of a hemiplegia in the great majority of these children. An additional discrete stenosis of the cervical portion of the internal carotid artery with distal intracranial arterial disease was demonstrated in 3 children, all of whom had had a recent nasopharyngeal infection. One child had bilateral intracranial internal carotid and renal artery disease prior to his hemiplegia, which followed a tonsillectomy. The concept of an undue sensitivity of the cerebral arteries or a pre-existing arteritis in some children is suggested, which, when associated with a nasopharyngeal infection or the effects of a systemic infection, results in an acute hemiplegia. This hemiplegia may thus be due to an arteritis itself or to associated thrombus and distal emboli.

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# SIZE, LOCATION, AND GRAVITATIONAL CHANGES OF NORMAL UPPER LOBE PULMONARY VEINS\*

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IN A previous study, the immediate cardiovascular response to exhaustive exercise was recorded on chest roentgenograms.¹ One group of volunteers demonstrated a striking increase in cardiac volume and upper lobe pulmonary vein engorgement. These changes were interpreted as an increase in cardiopulmonary blood volume and indicated a relative failure of myocardial adaptation to severe stress. Normal response to exercise has been indicated by Phillips et al.⁴ as a decreased transverse cardiac diameter, and by Levinson et al.² as an unchanged cardiopulmonary blood volume.

A roentgenographic method for assessing myocardial function was proposed, utilizing cardiovascular changes in chest roentgenograms. Further investigations were proposed, studying cardiovascular changes in the chest roentgenograms of athletes and of patients with known cardiac disease. The reliability of results in future investigations depends on the efficacy of evaluating the upper lobe pulmonary veins.

Several anatomic considerations in evaluating upper lobe pulmonary veins were contemplated:

- 1. At what level are upper lobe veins most easily identified on a chest roentgenogram?
- 2. What are the relative positions and directions of upper lobe arteries and veins?
- 3. Are upper lobe veins normally identified in the upright position?
- 4. Are upper lobe veins significantly altered by changes in posture?

An attempt to answer these questions forms the basis for this report.

#### MATERIAL AND METHOD

Fifty venous angiocardiograms obtained in the recumbent position and 50 examinations performed in a sitting position were reviewed. Records of medical histories, physical examinations, and cardiovascular investigations were evaluated in order to exclude patients with known cardiovascular disease. For the most part, the venous angiocardiographies were performed to rule out the presence of pulmonary emboli.

Opacified pulmonary vessels were measured at both the main pulmonary artery and aortic arch levels. The level of vessel bifurcation was determined. The incidence of vessel size too small to measure was noted.

#### RESULTS

Opacified upper lobe pulmonary veins were easily identified and measured at the level of the main pulmonary artery. Upper lobe veins bifurcated at a level between the main pulmonary artery and aortic arch in 40 per cent of examinations (Tables I and II).

In the upright position, pulmonary vein diameters varied considerably at both main pulmonary artery and aortic arch levels:

TABLE I
DIRECTION OF UPPER LOBE VESSELS

	Right Lung (per cent)	Left Lung (per cent)
Artery vertical	40	90
Artery oblique	60	10
Vein vertical	50	70
Vein oblique	50	30

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From the Departments of Radiology and Medicine, Vanderbilt University Hospital, Nashville, Tennessee. Supported by Cardiovascular Program Project Grant No. HE-08195.

	T	<b>BL</b>	ΕII		
RELATIVE	POSITION	ΟF	UPPER	LOBE	VESSELS

	Right Lung (per cent)	Left Lung (per cent)
Artery lateral	5	15
Vein lateral Artery and vein	95	85
superimposed	40	50

Main pulmonary artery level: too small to measure-15 mm.

Aortic arch level: too small to measure-6 mm.

The angiocardiograms were exposed at a 40 inch target-film distance, in both supine and sitting positions.

A significant difference in luminal diameters of opacified upper lobe veins in both the supine and sitting positions was noted (Fig. 1). The mean pulmonary vein diameters (main pulmonary artery level) were 7 mm. in the supine position and 4 mm. in the sitting position. A smaller mean pulmonary vein diameter in the full upright position is reasonably assumed.

#### CONCLUSIONS

In the upright chest roentgenogram, the normal upper lobe pulmonary veins are usually too small to identify. The frequency of their identification is about 7 per cent.3 In this study, considerable variation in the diameters of opacified upper lobe pulmonary veins was noted (too small to measure-15 mm.). The wide range of variation can be attributed to the variable state of vasomotor tone of small pulmonary vessels in normal individuals. One can conclude that, occasionally, an upper lobe pulmonary vein may be identified in the chest roentgenogram of an individual who does not have pulmonary venous hypertension or redistribution of pulmonary blood flow related to disease. A review of the range of normal variation suggests that a pulmonary vein diameter greater than 8 mm. (main pulmonary artery level) is abnormal.

Significant gravitational changes in pul

monary vein diameters have been demonstrated (Fig. 1). The explanations of the mechanisms involved in gravitational changes are conflicting. Whether the pulmonary veins are passive manometers of hydrostatic pressure or undergo reactive changes causing perfusion redistribution is uncertain. Considerable evidence has accrued indicating that pulmonary venous activity can be initiated by a variety of stimuli. Regardless of the mechanism, a change in the diameter of upper lobe pulmonary veins or initial recognition of upper lobe pulmonary veins in serial chest roentgenograms is considered abnormal and reflects abnormal response of the cardiovascular system to stress.

Our observations indicate that the upper lobe pulmonary veins are best visualized at the level of the main pulmonary artery, because of the frequency of bifurcation above this level. Pulmonary arteries and veins are most likely to be vertical in the upper lobe (90 per cent of arteries and 70 per cent of veins). In the right upper lobe, the likelihood of a vertical or oblique vessel direction is equal. The direction of the pulmonary vein (vertical or oblique) bears no

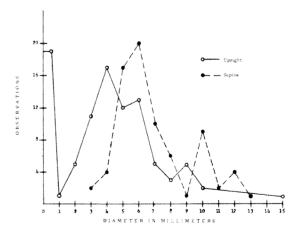


Fig. 1. Mean pulmonary vein diameter in supine position is 7 mm. and in sitting position is 4 mm. (at the main pulmonary artery level). Note that over one-third of opacified pulmonary veins, in sitting position, were too small to measure. Gravitational differences in pulmonary vein diameters are statistically valid. Target-film distance, 40 inches.

constant relationship to the direction of the ipsilateral artery.

The position of the upper lobe vein, in relation to the ipsilateral artery, is either superimposition (40 to 50 per cent of instances), or the vein is almost invariably lateral to the artery (85 to 95 per cent of instances, if the vessels are side-by-side). The failure to consistently identify dilated upper lobe pulmonary veins in patients known to have pulmonary venous hypertension is probably related to the frequency of superimposition of the upper lobe artery and vein.

#### SUMMARY

In a previous study, the upper lobe pulmonary venous distention after exhaustive exercise was assessed in chest roentgenograms. The efficacy of evaluating upper lobe veins in future studies depended on several anatomic considerations.

Fifty venous angiocardiograms obtained in the recumbent position and 50 examinations performed in the sitting position were reviewed. The opacified pulmonary vessels were measured at main pulmonary artery and aortic arch levels. The level of vessel bifurcation and the vessel direction were tabulated. The relationship between artery and ipsilateral vein was noted. Comparison of vein size in the recumbent and sitting positions was made.

The upper lobe pulmonary veins are most consistently visualized at the main pulmonary artery level. Superimposition of artery and vein occurs in 40 to 50 per cent of examinations; otherwise, the vein is almost invariably lateral to the artery. The pulmonary vessels are most likely vertical in the left upper lobe and either vertical or

oblique in the right upper lobe. The upper lobe veins vary considerably in diameter, and bifurcate below the aortic arch level in 40 per cent of the examinations. Significant gravitational changes in normal pulmonary vein diameters occur.

Although the normal upper lobe pulmonary veins are usually too small to identify, detection of upper lobe pulmonary veins on a chest roentgenogram does not necessarily indicate pulmonary venous hypertension or flow redistribution. However, considerable significance can be ascribed to the initial detection or to the diameter change of the pulmonary veins in serial chest roentgenograms. The failure to consistently identify upper lobe veins in patients known to have pulmonary venous hypertension is probably related to the frequency of superimposition of the artery and vein.

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# DETERMINATION OF IN VIVO PERSISTENCE OF TANTALUM DUST FOLLOWING BRONCHOG-RAPHY USING REACTOR-ACTIVATED TANTALUM AND TOTAL BODY COUNTING\*

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THE use of bronchography in clinical medicine has always been limited by the contrast media available. Ideally, a contrast medium for bronchography should be inert and nonirritating, highly radiopaque, easily administered, and completely cleared from the bronchial tree within 24-48 hours. Of the bronchographic media presently in use, none satisfies all these criteria. Excellent topical anesthesia must be obtained to prevent respiratory irritation and subsequent expectoration of the contrast medium. Excess oil, acting as a vehicle for the contrast material, may decrease its radiopacity. Iodine-containing agents may be dangerous to hypersensitive individuals, while some bronchographic media may produce undesirable effects such as oil granulomata or chemical pneumonias.

Recently, tantalum dust has been suggested by Nadel and co-workers<sup>3</sup> as a suitable radiopaque material for bronchography. Tantalum dust may be administered as an aerosol, thus avoiding some of the irritative effects of liquid contrast media. The possibility of clinical administration of tantalum by simple inhalation has also been raised.

Tantalum is chemically inert and highly radiopaque, having a greater density than either iodine or barium (16.8 gm./cc.³ for Ta, vs. 4.19 gm./cc.³ for I and 3.5 gm./cc.³ for Ba). Because of the correspondingly higher absorption coefficient of tantalum,

a much smaller quantity results in the same degree of bronchial opacification. The safety of tantalum is based on its longterm use in tissue prostheses and its assumed rapid clearance from the lungs. Prolonged retention with unexpected local tissue reaction to the particulate dust might have unfavorable consequences. Quantitative measurements of retained tantalum dust in the living subject have not been reported. While chest roentgenographic appearances provide a rough indication of the persistence of tantalum, and postmortem study may reveal its persistence at a specific point in time, these methods alone do not give a complete picture of pulmonary clearance. The present study was undertaken to determine clearance rates following experimental bronchography.

#### METHOD

Three different samples of stable tantalum (Ta<sup>181</sup>) dust,\* with particles having count mean diameters of approximately 1.0, 5.0 and 50 microns, were obtained. Four to 5 gm. aliquots of each sample were activated in the UCLA reactor. The final specific activity of the 5  $\mu$  and 50  $\mu$  samples was approximately 2  $\mu$ c/gm., while that of the 1  $\mu$  sample was approximately 4  $\mu$ c/gm. Since activation time in the reactor was relatively short (20–35 min.), virtually all

<sup>\*</sup> Fansteel, Inc., Metals Division, Baltimore, Maryland.

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the activity could be attributed to Ta<sup>182</sup>, which has a 115 day half-life.

The following equations summarize the reactions:

$$^{1}_{0}n$$
 (thermal) +  $_{73}Ta^{181}$   $\longrightarrow_{73}Ta^{182}$   $_{73}Ta^{182}$   $\longrightarrow_{74}W^{182}$  +  $\beta^{-}$  +  $\gamma$ .

Longer irradiation times would have led to increased production of Ta<sup>183</sup>, which has an undesirable 5 day half-life.

The activated tantalum was delivered into anesthetized 15-18 kg. mongrel dogs via a No. 6 French catheter introduced through an endotracheal tube under fluoroscopic control. The apparatus used to deliver the activated tantalum dust is represented schematically in Figure 1. It is a closed system with valves to prevent exhalation of radioactive aerosol. As a precaution, the investigators were half-face respirators during all experiments. A low-volume air sampler was operated during administration of the radioactive tantalum, and the calculated aerosol concentration did not exceed the maximum permissible concentration set by the State of California  $(7 \times 10^{-10} \mu c/ml.)$ .

Six animals were used, 2 animals for each of the 3 different tantalum particle sizes. Chest roentgenograms and total body counts (using the Center for the Health Sciences Total Body Counter) were performed immediately following the bronchographies and periodically thereafter. After correcting for physical decay of the activated tantalum, an *in vivo* retention curve was obtained for each animal.

The animals were sacrificed when it became clear that very little further excretion of the tantalum was occurring (5  $\mu$  and 50  $\mu$  animals after 110 and 205 days, and 1  $\mu$  animals after 70 and 165 days). After sacrificing, the whole body, and then the thoracic contents (including heart, lungs, regional lymph nodes, and other mediastinal structures) and the individual lungs of each animal, were counted. Following these determinations of residual tantalum activity, the thoracic contents were roentgeno-

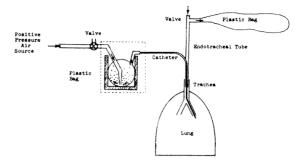


Fig. 1. Schematic drawing of apparatus.

graphed (30 kv. at 3 ma., for 1 3/4 min.). Histologic sections were also obtained from the lungs and hilar lymph nodes.

In order to determine the amount of tantalum delivered to each animal during bronchography, a "phantom dog" was devised. By comparing the results with initial whole-body counts on the bronchography subjects, the amount of tantalum initially retained in each animal for the diagnostic bronchogram was estimated.

#### RESULTS

Because of limitations in mobility with the closed delivery system used for activated tantalum, the quality of the resulting bronchograms was not as satisfactory as when nonradioactive dust was used (Fig. 2). Figure 3 shows the total body retention of tantalum in the initial 10 days following bronchography with the 3 different particle sizes. After a short initial delay in clearance, there was rapid fall-off in retained tantalum during the first 3 days. Subsequent total body counts revealed very slow removal of the remaining tantalum with substantial retentions in 5 out of the 6 animals tested. Except for I animal receiving 50  $\mu$  particles, the animals retained between 6 and 20 per cent of the originally administered tantalum for periods of from 70 to 150 days (Fig. 4). The exceptionally low retention in I animal might have been predicted after viewing the bronchogram, which was of poor quality. Because of repeated plugging of the catheter, very little tantalum reached the deep lung compartments in this animal.

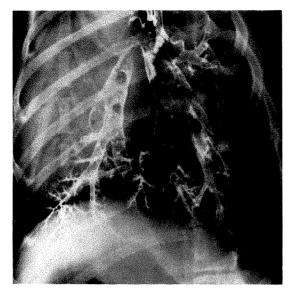


Fig. 2. Bronchogram obtained with Ta<sup>182</sup> and closed-system administration.

If an exponential fall-off is assumed for the slow clearance after 7 days, biologic half-times may be calculated for the remaining tantalum. Table 1 shows calculated biologic half-times ranging from 105 to 817 days. The localization of the retained tantalum, based on counts obtained after sacrificing the animals, is shown in Table 11. Lung percentages were slightly greater than 100 per cent (based on total activity of the thoracic contents), because of the lack of scattering and absorption by other tissues when the lungs alone were counted.

Calculation of the initial retained mass of tantalum following bronchography, using the phantom dog as a model and the

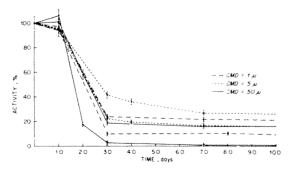


Fig. 3. Graph of total body  $Ta^{182}$  retention in first 10 days after bronchography. CMD=Count Mean Diameter;  $\mu$ = micron.

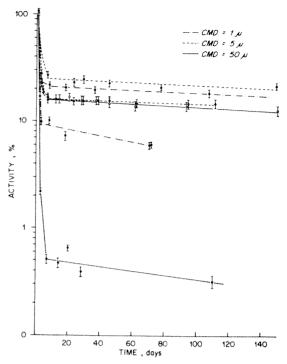


Fig. 4. Long-term total body Ta<sup>182</sup> retention curves.

initial total body counts, gave values ranging from 3-6 gm.<sup>1</sup>

Roentgenograms of the thoracic contents after sacrifice revealed residual tantalum deposits (Fig. 5). Histologic sections from the animal lungs showed particulate tantalum free in alveoli as well as contained within macrophages, with minimal tissue reaction. No particulate tantalum could be found in the mediastinal lymph nodes examined.

Table I
BIOLOGIC CLEARANCE TIMES

Dog No.	Particle Size (count mean diameter in microns)	Clearance Half-times* (after 7 days)	Standard Error of the Estimate
I	5.0	817 d	0.167
2	5.0	652 d	1.75
3	50	542 d	0.266
4	50	143 d	
5	1.0	105 d	1.24
6	1.0	590 d	0.362

<sup>\*</sup> Exponential clearance is assumed.

TABLE II
DISTRIBUTION OF RETAINED TANTALUM

			Ta <sup>182</sup> Activity at Sacrifice						
Dog No.  Particle Size (count mean diameter in microns)	Time of Sacrifice (days post- broncho- gram)	Per Cent of Total Initial Activity*		Per Cent Present at Sacrifice					
		Total Body	Carcass†	Total Body	Carcass†	Thoracic Contents	Lungs (as per cent of thoracic contents)‡		
I	5.0	111	1.5	0.02	100	0.13	99.9	IOI	
2	5.0	205	20	0.5	100	2.4	97.6	104	
3	50	204	13	0.3	100	2.3	97.7	107	
4	50	110	0.3	0.05	100	16	84.0	103	
5	1.0	7 I	6	0.5	100	2.7	97.3	100	
6	I.O	164	18	0.2	100	1.0	99.0	103	

\* Corrected for physical decay.

† Defined as total body minus thoracic contents.

‡ Greater than 100 per cent because of less scattering and absorbing material for lungs alone.

#### DISCUSSION

The amounts of tantalum initially retained following diagnostic total bronchograms in medium sized dogs is estimated to be 3–6 gm. The rapid initial clearance of tantalum from the respiratory tree (Fig. 3) is attributable primarily to the ciliarymucous transport system, which has been designated as "Phase I" by the Task Group on Lung Dynamics for Committee II of the International Radiological Protection Commission.<sup>2</sup> Tantalum particles raised from the lower respiratory tract in this phase are subsequently swallowed, and their ensuing intestinal passage accounts for the short initial delay in total-body clearance.

The slower component of the clearance curves after 7 days (Fig. 4) reflects primarily the pulmonary component, or clearance from the distal nonciliated portions of the respiratory tree. Clearance from the lung during this period, designated "Phase II" in the Task Group report, is mainly by means of lymphatic or blood-vascular transport. Also, there is some late local clearance of the particles by macrophages, which is in turn coupled with the ciliary-mucous transport system.

The data agree reasonably well with a report by Sill *et al.*, 4 of an accidental human exposure to unsized particles of radioactive tantalum oxide, following air-borne release of the tantalum from a contaminated tubing in a reactor experiment. In that report, 93 per cent of the tantalum was excreted in the first 7 days. Although the authors were unable to make a precise statement of biologic half-life of the remaining tantalum



Fig. 5. Roentgenogram of thoracic contents from autopsied animal.

(i.e., after 7 days) they concluded that it was "undoubtedly greater than 1,000 days."

Counts of autopsied canine lungs, compared to the total body, indicated that most of the retained tantalum remained within the lungs (Table II). This was supported by the specimen roentgenograms (Fig. 5).

No systematic relationship between *in vivo* persistence of activated tantalum and the administered particle size could be demonstrated. However, there was unexpected long-term retention of activated tantalum in 5 out of 6 animals. The persistence of activated tantalum in experimental bronchography suggests caution in the use of tantalum dust in humans, if use of this agent is based in part on the assumption that it is rapidly and completely cleared from the bronchial tree. Obviously, the above cautionary note applies strictly only to the technique of administration and to the particle sizes employed in these studies.

#### SUMMARY

A convenient experimental method for the *in vivo* estimation of retained metallic substances, using neutron activation prior to their administration and subsequent total body counting, has been applied successfully in this study.

Unexpectedly long persistence of tantalum dust suggests caution in the use of this agent.

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# DEMONSTRATION OF A RETROGRADE PANCREATIC PATHWAY: CORRELATION OF ROENTGENO-GRAPHIC AND ELECTRON MICROSCOPIC STUDIES\*

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HERRING and Simpson believed that following ligature of the duct of Wirsung pancreatic secretions continue but escape by lymphatics and blood. Byrne and Boyd<sup>1</sup> postulated retrograde absorption of pancreatic fluid injected into the pancreatic ducts. Evidence for such a ducto-interstitial-venous pathway was presented by Stein et al.4 In 1957 Edlund and Ekholm<sup>2</sup> demonstrated a basement membrane lined interstitial space in the pancreas which they thought might afford a pathway for retrograde flow from ductule to capillary without direct pancreatic cellular contact. Waldron<sup>5</sup> has observed consistent retrograde pancreatic passage of the water soluble roentgenographic contrast agent, sodium diatrizoate, in dogs. The initial observation that a pyelogram occurs rapidly after initiating flow of sodium diatrizoate into the pancreatic ductal system (Fig. 1, A and B) was followed up by a correlative electron microscopic study.

This paper is submitted as documentation of a pancreatic ducto-interstitial-venous pathway studied by means of roentgenography and electron microscopy.

#### METHOD

Laparotomies were performed under intravenous pentobarbital anesthesia in 30 to 40 pound mongrel dogs of both sexes. Following duodenotomy the pancreatic duct opening was identified and cannulated with a No. 5 French ureteral catheter. Five ml. of contrast material (sodium diatrizoate

[hypaque 50] or a combination of 4 ml. hypaque 50 with 1 ml. thorotrast) was infused at a pressure of 150 cm. of water. Roentgenograms were made immediately prior to biopsy to obtain a record of the pancreatic opacification which had resulted from the infusion (Fig. 2, A and B). Simultaneous biopsies of the body of the proximal pancreatic lobe and the left kidney were fixed immediately for electron microscopy. They were minced into small blocks about I mm. in greatest diameter and placed in 3 per cent glutaraldehyde in o.1 M cacodylate buffer followed by postosmication in I per cent osmium tetroxide in the same buffer, or were placed in I per cent buffered osmium tetroxide without preceding aldehyde fixation. The fixed tissue was rapidly dehydrated in ethanol and embedded in Swiss Araldite. Thin sections were cut on a diamond knife with a Porter-Blum MT-1 microtome, stained with lead citrate and examined in an RCA EMU-3F or 4A electron microscope.

#### RESULTS AND DISCUSSION

The triiodinated roentgenographic contrast material, sodium diatrizoate (hypaque 50), used in this study is used widely in clinical radiology. This compound was found to be electron opaque and was observed in the pancreatic ductules in the specimens obtained immediately following pancreatic infusion (Fig. 3). Simultaneous renal biopsy showed the electron opaque sodium diatrizoate in the brush

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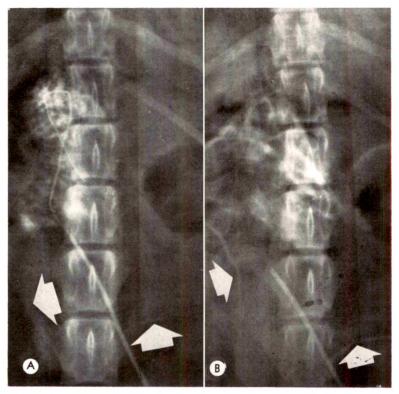


Fig. 1. (A) Pancreatogram after total of 9 ml. of sodium diatrizoate had been infused in 3½ minutes at an infusion pressure of 150 cm. of H<sub>2</sub>O shows proximal lobe ductal and glandular opacification and early visualization of both ureters (arrows). (B) Ten minutes after instillation of a total of 22 ml. of sodium diatrizoate in 8½ minutes. Pancreatic opacification is barely visible and the pelvocalyceal and ureteric systems are now well demonstrated (arrows). Although opacification of the pelvocalyceal and ureteric collecting systems was not as striking with the 5 ml. quantities of sodium diatrizoate used in the current study, it was present (Fig. 2).

border of the proximal convoluted tubule (Fig. 4). Although the electron density of the contents of the pancreatic ductules was distinctly greater than in the pancreas of control noninfused dogs, it was not possible to follow it beyond the lumen of the ductule. Therefore thorotrast was added to the hypaque as an electron dense indicator of the distribution of the contrast material after infusion into the pancreatic duct. It was readily visible as extremely electron opaque particles that extended into the interstitial spaces between the pancreatic cells and into the perivascular spaces (Fig. 5, A and B). Occasionally thorotrast was identified in pinocytotic vesicles in the capillary endothelium and rarely as small aggregates in a vessel lumen. At the pressures used in these ex-

periments (150 cm. H<sub>2</sub>O) rare pancreatic cells showed traumatic penetration by the injected radiographic media.

The observation that iodine containing roentgenographic contrast agents can be visualized with the electron microscope is one which presents far-reaching possibilities for multiple static views of rapidly evolving physiologic processes. In the current study it has been instrumental in demonstrating a pancreatic pathway which had been postulated earlier (Fig. 6). Several methods for obtaining retrograde pancreatography are in developmental stages. The utilization of the ductointerstitial-venous pathway for rapid retrograde passage of water soluble roentgenographic contrast agents permits pancreatic opacification with minimal direct pan-

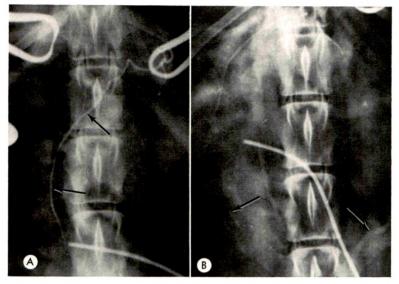


Fig. 2. (A) Roentgenogram showing pancreatic ductal opacification (arrows) and no urinary tract opacification after 5 ml. of sodium diatrizoate. Simultaneous pancreatic and renal biopsies were taken immediately following this roentgenogram. Figure 3 shows electron micrograph of pancreas. (B) Roentgenogram 2 minutes following pancreatic and renal biopsies shows diminished opacification in the pancreatic duct and contrast material now present in both pelvoureteric systems (arrows).

creatic cellular contact to the contrast media. It is thought that the utilization of this pathway makes instillation of sodium diatrizoate in retrograde pancreatography safe—a finding indicated by previous animal toxicity studies.<sup>5</sup> Our observation of focal injury to some pancreatic cells at an injection pressure of 150 cm. H<sub>2</sub>O

Fig. 3. Electron micrograph of a section through the body of the proximal pancreatic lobe. Electron opaque sodium diatrizoate is seen in a pancreatic ductule (arrow).

suggests that in the human being injections should be made at a lower pressure.

That other contrast agents may be toxic is suggested by our preliminary results with ethiodol, an ethiodized oil which causes obstruction of pancreatic ducts. Indeed, the pancreas could still be demonstrated roentgenographically 5 days after an infusion of this agent. The ducto-interstitial-venous pathway was rapidly blocked at

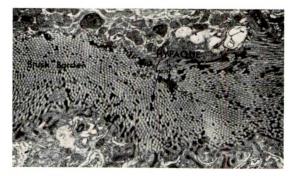
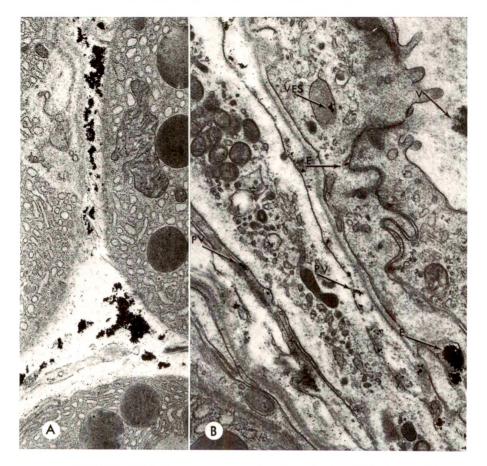


Fig. 4. Electron micrograph of the brush border of the proximal convoluted tubule of the kidney obtained at the same time as the pancreatic section illustrated in Figure 3. Here the electron opaque sodium diatrizoate can be seen with even greater clarity than in Figure 3.



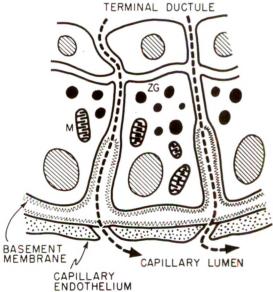


Fig. 6. Diagrammatic illustration based on Edlund and Ekholm's work to illustrate the ducto-interstitial-venous pathway that was postulated to explain the rapid passage of sodium diatrizoate

the ductule level since no electron opaque material was demonstrated in the kidney and no pyelogram was produced.

#### SUMMARY

Water soluble contrast material infused into the pancreatic duct is followed rapidly by roentgenographic visualization of the urinary tract in the dog. Iodinated contrast materials have been found to exhibit the property of opacity on electron micrographic study so that their location can be established. Biopsy specimens of the pancreas obtained at the time of infusion of contrast material demonstrated opaque material on electron microscopic evaluation. Simultaneous renal biopsies showed

through the pancreas. A basement membrane lined interstitial space extends from the pericapillary area to, at least, the proximity of the terminal ductules. M=mitochondria; ZG=zymogen granuoles.

Fig. 5. (A) Electron micrograph showing dense thorotrast particles in the interstitial space between 3 pancreatic acinar cells. (B) Electron micrograph of blood vessel in exocrine pancreas. Part of an acinar cell with a single zymogen granule is present at the lower left. The arrows PV indicate thorotrast in the perivascular space. At VES a vacuole in the endothelial cytoplasm contains thorotrast. Arrows (E) show small and large aggregates of thorotrast in the space between 2 endothelial cells. A few isolated particles also are evident within the lumen at (V).

**→** (((()

similar material in the brush border of the proximal convoluted tubule before it was visible roentgenographically.

Evidence is presented to document the pancreatic ducto-interstitial-venous pathway postulated in 1909 by Herring and Simpson.<sup>3</sup>

The observation that iodine containing roentgenographic contrast agents are visualized with the electron microscope offers wide possibilities for obtaining multiple static views of rapidly evolving physiologic processes.

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# THE KINETICS OF CELLULAR PROLIFERATION IN NORMAL AND MALIGNANT TISSUES: A REVIEW OF METHODOLOGY AND THE ANALYSIS OF CELL POPULATION KINETICS IN HUMAN TISSUES\*

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NORMAL and tumor cell population growth in vivo has been estimated quantitatively in experimental animals and in humans by a variety of methods.<sup>3,15</sup> The most valuable for analyzing cell population kinetics,\* i.e., the dynamic aspects of cell populations which regulate the rates of cell production and cell loss, has been the incorporation of specific nucleic acid precursors combined with high resolution autoradiography.4,14,15,20,23 TdR and UR are nucleic acid precursors which are incorporated into proliferating cells synthesizing DNA and preparing for division or into RNA in cells undergoing proliferation and differentiation, respectively. The resulting cellular labeling provides valuable

\* The following abbreviations are used in the analysis of cell opulation kinetics20: C, cells in cell cycle; M, cells in mitosis (M phase); G1, cells in pre-DNA synthesis phase; S, cells in DNA synthesis (S phase); G2, cells in post-DNA synthesis phase; Go, potentially proliferative cells; S, stem cell compartment; P, proliferative cell compartment; D, transitional, maturing and differentiating cell compartment; F, functional cell compartment; N, number of cells in the population;  $N_e$ , number of cells in the population in cell cycle;  $N_0$ , number of cells in the population at time 0; Nt, number of cells in the population at time t; N<sub>s</sub>, number of cells in the population in DNA synthesis; N<sub>m</sub>, number of cells in the population in mitosis; t<sub>e</sub>, duration of the cell cycle; tm, duration of the M phase; tg1, duration of the  $G_1$  phase;  $t_s$ , duration of the S phase,  $t_{g_2}$ , duration of the  $G_2$  phase; m, mitotic rate, *i.e.*, the number of cells dividing per hour: LI, TdR-H3 labeling index (Ns/N); k, cell flux in and out of a proliferative compartment; ki, cell influx into a compartment;  $k_{j}$ , cell efflux out of a compartment;  $\lambda$ , growth rate constant; T, tissue doubling time; Tlin, tissue doubling time for linear growth rate characteristics (rectangular cell phase distribution); Texp, tissue doubling time for exponential growth rate characteristics (exponential cell phase distribution); Tint, tissue doubling time for growth rate intermediate between linear and exponential characteristics (intermediate cell phase distribution); TdR, thymidine; TdR-H3, tritiated thymidine; TdR-C14, carbon 14 labeled thymidine; UR, uridine; UR-H3, tritiated uridine.

information on the proliferation and differentiation capacities of the cell population.

Recent reports from this laboratory<sup>5-10</sup> described studies on reliable methods for the *in vitro* incorporation of labeled nucleic acid precursors into human tissues of surgical and biopsy specimens obtained from clinical patients. Under controlled laboratory conditions the incorporation of the label occurred only in those cells which are synthesizing DNA or RNA in the patient, thereby providing a pattern of labeling similar to that obtained by in vivo methods.<sup>10</sup> The present investigation concerns an appraisal of these techniques, and an analysis of the kinetics of cellular proliferation in human tissues based on the quantitative histologic data for determining the proliferative capacities and potential growth rates in normal and diseased, and particularly, neoplastic cell populations in vivo.

#### MATERIAL AND METHOD

#### BACKGROUND TO EXPERIMENTAL DESIGN

The work to be reported is part of a broad study on quantitative aspects of cellular proliferation in normal and neoplastic human tissues. Emphasis is placed on 4 important problems: (1) How rapidly do cells proliferate in normal and diseased human tissues? Do neoplastic tissues proliferate faster than cells in the tissue of origin, or cells of the tissue surrounding the tumor? (2) What kinetic factors at the cellular level contribute to the over-all

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growth of a neoplasm in terms of cell cycle time, growth fraction and cell loss due to emigration or death? (3) To what extent are these factors important in those normal and abnormal tissues which appear similar histologically, but have widely different growth rates? (4) How does cell proliferation and differentiation in a benign lesion compare with a malignant one, and in a primary neoplasm with its distant metastasis within the body?

The metabolic activities in proliferating human tissues which concern nucleic acid synthesis and the cell cycle are being examined by quantitative histologic techniques, primarily high resolution autoradiography following incorporation of labeled nucleic acid precursors. The tissue turnover rates, potential tissue doubling times, and the temporal patterns of DNA and RNA synthesis in relation to the cell cycle of the proliferating cell populations are determined by appropriate techniques using H3-labeled and C14-labeled TdR and UR. Quantitative information on cell population kinetics in normal, inflammatory, and neoplastic tissues of the larynx and adjacent tissues from a selected group of over 200 patients is presented, and the experimental data are discussed in terms of relationships of tissue turnover times, proliferative capacities, and growth rates of human cell populations in vivo. Details concerning the human tissue specimens, animal experiments for standardization of the in vitro technique, culture media, labeled DNA and RNA precursors, hyperbaric oxygen chambers, temperature and pH requirements, high resolution autoradiography, and quantitative histologic analysis have been described in detail in previous publications.5-10 These will be summarized briefly here, but for more detailed descriptions of the techniques and facilities used, the previous reports should be reviewed.

#### HUMAN TISSUE SPECIMENS

Small surgical and biopsy specimens were obtained in the operating or endos-

copy rooms, placed immediately in ice-cold (4°C.) medium, brought to the laboratory within 1 to 2 hours and cut into small pieces (~1 mm.8) for incubation.

## CULTURE MEDIUM AND LABELED NUCLEIC ACID PRECURSORS

Medium M-199,\* Earle base (20.0 ml., pH 7.0±0.2) with 20 per cent fetal calf serum (4.0 ml., pH range 7.2-7.8) was used; the final pH of the culture medium was  $7.5 \pm 0.2$ . For pulse-labeling studies, TdR-H3 (specific activity 14.5-16.5 Ci/ mmole,† 1.0 µCi/ml. in 0.9 per cent NaCl) or UR-H<sup>8</sup> (specific activity >20 Ci/ mmole, 1.0 µCi/ml. in 0.9 per cent NaCl) was added to the medium, depending on the experiment. For double-labeling experiments, M-199 medium (4.17 ml.) with fetal calf serum (0.83 ml.) and TdR-H<sup>8</sup> (0.025 ml., 0.5 μCi/ml.) was used; tissue specimens were incubated for 55 minutes, thoroughly washed twice with cold TdR medium for 5 minutes, and then incubated in fresh M-199-fetal calf serum medium and TdR-C14 (specific activity 53.8 mCi/ mmole, 0.05 ml., 1.0  $\mu$ Ci/ml. in 0.9 per cent NaCl).

#### HYPERBARIC OXYGEN INCUBATION

Under normal atmospheric conditions, the cells in small tissue biopsy specimens are relatively anoxic, and, while TdR and UR were available to all cells deep within the tissue, only those cells sufficiently oxygenated by diffusion from the medium appear to retain the capacity to incorporate and utilize the nucleic acid precursors.10 This has been demonstrated to be more critical for the DNA than for the RNA precursor. The rationale for incubating under hyperbaric oxygen conditions was to increase the pO<sub>2</sub> within the tissue, and thereby increase the depth of incorporation of TdR and UR. Tissue specimens were therefore cut into ~1 mm.8 pieces or less, and incubations were carried out in specially

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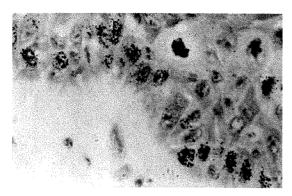


Fig. 1. Autoradiograph of a rapidly proliferating contact ulcer squamous granuloma from the larynx of a 52 year old man. Cells in DNA synthesis and mitosis are readily identified. Cell loss due to desquamation is extensive, and controls the growth rate (1,200 ×; H and E; TdR-H³).7

designed hyperbaric oxygen chambers under 100 per cent O<sub>2</sub> at 2,280 mm. Hg pO<sub>2</sub>, and a flow rate of 500 cc./min., in agitated medium at 37.5°C., and pH~7.5.

### AUTORADIOGRAPHY AND QUANTITATIVE HISTOLOGY

After incubation, specimens were fixed for 24 hours (20 parts 70 per cent ethanol, 2 parts 10 per cent formalin, CaCO3 in excess, and I part glacial acetic acid). Histologic sections (4 \mu thick) were cut from waxembedded tissues. Slides were dipped in Kodak NTB2 nuclear emulsion,\* exposed at 4°C. for 3 to 4 weeks, developed in Kodak D19 solution,\* fixed in Kodak fixer,\* and stained with hematoxylin and eosin. In representative tissue samples, labeling indices were determined as a percentage of all nuclei of cells (in counts of 1,000 to 2,000 cells) of a morphologically defined population in the tissue specimen. Under these experimental conditions, there was no evidence of deleterious effects due to the high pO2 or to beta radiation from intranuclear H<sup>3</sup> which could affect the incorporation of labeled nucleic acid precursor in vitro.

#### RESULTS

#### SITES OF CELL PROLIFERATION

The specimens examined in the present study comprise 87 of 102 patients with

\* Eastman Kodak, Inc., Rochester, New York.

clinical disease of the larvnx and adjacent structures classified into 4 groups: normal; inflammatory lesions; benign neoplasms (squamous cell papillomas of the larynx); and malignant neoplasms (squamous cell carcinomas of the larnyx). TdR-H3 was available to all proliferating cells and readilv labeled cells in DNA synthesis. In normal tissues, labeling was uniformly distributed throughout the zones of proliferation, e.g., in the germinal layer of the stratified squamous epithelium of the larynx. In inflammatory and neoplastic tissues, cell labeling did not occur uniformly, and there was a variation in the percentage of cells labeled in different regions of the same specimen. In inflammatory tissues, higher labeling indices were associated with regions of acute inflammatory cell infiltration, primarily polymorphonuclear leukocytes (Fig. 1). In neoplasms, clusters of labeled cells at different sites of the same tumor biopsy specimen were characteristic in carcinoma (Fig. 2). These observations in tumors may be related to a number of factors. For example, cells with similar generation times may represent clones of tumor cells. and greater labeling indices would occur in populations with relatively short cell cycle times. Due to variation in metabolic conditions throughout the diseased tissue, and particularly in tumors, the size of the

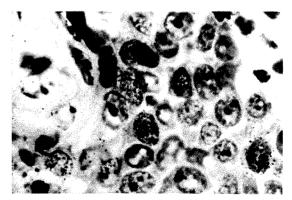


Fig. 2. Autoradiograph of rapidly growing squamous cell carcinoma from the larynx of a 66 year old man. Cells label in clusters; proliferating regions form active zones of neoplastic growth. Cell loss to desquamation is extensive (2,000 ×; H and E; TdR-H³).

growth fraction<sup>16</sup> would depend, to a large extent, on the location of cells within the tissue. Further, a greater proportion of proliferating cells occurs in the advancing or growing edge of a tumor. Clusters of proliferating cells would be more common nearer the surface of the growing tissue, and this is the usual site of a biopsy specimen.

There was some evidence of preservation of cellular differentiation in normal tissues in the *in vitro* situation. Under prolonged incubation periods, labeled cells were able to leave the germinal layer and migrate toward the surface within 4 to 6 hours, but still were unable to divide. This provided evidence that in the *in vitro* environment, proliferating cells piled-up in the post-DNA synthesis period and did not proceed through cell division, but without inhibition of synthesis of substances which produced differentiation.

#### RATES OF CELL PROLIFERATION

Tables I to IV summarize the kinetic data obtained on the tissue specimens studied. Labeling of a percentage of normal and abnormal epithelial cells occurred in all specimens, and it was possible to obtain a reliable TdR-H³ labeling index for all tissues. The percentage labeling indices

 $T_{\rm ABLE} \ I$  kinetic parameters for normal Larynx  $(t_s \! = \! 12.5 \ hr.)$ 

Sex/Age	LI (per cent)	$T_{\rm lin}$	$T_{\mathrm{int}}$	$T_{\rm exp} \ (hr.)$
M/9 yr.	7.6	164	131	_
M/10 yr.	7.2	174	130	-
F/12 yr.	6.9	181	145	_
F/39  yr.	4.9	254	203	_
$M/_{46}$ yr.	6.2	201	161	_
M/60 yr.	5.3	236	177	

varied widely among the different tissues, but the range for tumors was within that for normal tissues, and frequently much less than those for inflammatory lesions, indicating that rates of cell proliferation were not necessarily greater in neoplastic as compared with normal or inflammatory tissues.

The rates of cell proliferation have been expressed as *potential tissue doubling times* (T); *i.e.*, the time for the cell population to double in the absence of cell loss. Provided certain assumptions are made, analysis of the kinetic data can provide valuable information on the range of rates of cell production or cell birth rates—from steady-state renewal kinetics to log phase expo-

Table II  $\label{table_table} Kinetic \mbox{ parameters for inflammatory tissues of larynx } \\ (t_{\text{s}}\!=\!12.5\ hr.)$ 

Sex/Age	Diagnosis	LI (per cent)	$T_{lin}$	$\mathrm{T_{int}}$	T <sub>exp</sub> (hr.)	
F/35 yr.	Hyperkeratosis	8.8	142	114	93 53 269	
F/38 yr.	Hyperkeratosis 15.3 Hyperkeratosis 3.0 Hyperkeratosis 9.9	15.3	81	66		
M/50 yr.		3.0	417	332 101		
F/54 yr.		9.9	126		8 <b>2</b> 66	
M/62 yr.	Hyperkeratosis	13.1	95	72		
F/63 yr.	r. Hyperkeratosis	yr. Hyperkeratosis	3.2	390	312	253
F/66 yr.	Hyperkeratosis	6.3	198	159	129	
M/67 yr.	Hyperkeratosis	6.2	201	151	139	
F/34  yr.	Vocal cord granuloma	Vocal cord granuloma 8.8	8.8	142	114	93
M/43 yr.	Vocal cord granuloma	9.1	137	103	95	
M/52 yr.	Vocal cord granuloma	72.4	17.2	13.7	ΙI	
F/28 yr.	Melanosis	14.5	86	69	56	

Table III

KINETIC PARAMETERS FOR SQUAMOUS CELL
PAPILLOMA OF LARYNX

 $(t_s = 15 \text{ hr.})$ 

Sex/Age	LI (per cent)	$T_{\mathrm{lin}}$	$T_{int}$	${ m T_{exp} \over (hr.)}$
M/8 yr.*	16.6	90.0	70.8	58.8
M/8 yr.*	5.6	266.4	213.6	172.8
M/8 yr.*	6.3	237.6	178.8	164.4
F/10 yr.	4.2	357.6	267.6	246.0
M/12 yr.	4.7	319.2	238.8	220.8
F/12 yr.	4.1	364.8	291.6	238.8
F/12 yr.	1.8	831.6	664.8	540.0
F/29 yr.	3·4	440.4	351.6	284.4
F/37 yr.	3.1	483.6	362.4	333.6
F/39 yr.	1.2	1,248.0	999.6	811.2
M/41 yr.	4.8	312.0	234.0	216.0
F/42 yr.	5.9	254.4	204.0	165.6
F/44 yr.	9.8	153.6	123.6	100.8
M/61 yr.†	10.2	146.4	117.6	97.2

<sup>\*</sup> Same boy with juvenile papillomas of larynx; biopsies taken 3 to 4 weeks apart.

nential growth. The following general observations may be noted. The range of T values for the *normal* epithelium of the human larynx is approximately 150 to 250 hours, and is slightly less in the child than in the adult tissue (Table 1). Inflammatory lesions have the shortest doubling times, frequently less than 100 hours (Table 11). Benign tumors have growth rates which vary widely, and may extend from 2 to 6 weeks (Table III). Malignant neoplasms have T values of the range of normal tissues, or about 150 to 250 hours, indicating that rates of malignant cell proliferation are not necessarily greater than normal cells from which they arise (Table IV).

## DURATION OF DNA SYNTHESIS PERIOD IN HUMAN TISSUES

The kinetic analyses which allow potential tissue doubling times to be predicted for measured values of TdR-H³ labeling indices require information on the duration of the DNA synthesis period (t₅). There are few data on the duration of the S period in human tissues—both normal and diseased, and particularly tumors. The values for

t<sub>s</sub> in human tissue biopsy specimens have been estimated in 13 patients using a double-labeling method adapted to the *in vitro* technique.<sup>5</sup> Table v lists the t<sub>s</sub> and T values; the following observations are noted. The range of t<sub>s</sub> values in human tissues is from ~10 to 25 hours, is greater for malignant than for benign tumor cells, and least for normal cells. The T values for malignant cells, based on measured values of t<sub>s</sub>, are necessarily greater than for benign tumor cells.

# ANALYSIS OF CELL POPULATION KINETICS CELL POPULATION KINETICS

The maintenance of a proliferating cell population in vivo is dependent on the balance between the rate of cell production and the rate of cell loss. A proliferating cell system can frequently be compartmentalized in relation to specific attributes of proliferation, maturation and function (Fig. 3). Stem cells which feed the proliferative compartment are self-maintaining, while providing progeny for the proliferating population. The proliferative compartment normally amplifies the cell population through sequential divisions; cells leaving this compartment give rise to transitional or differ-

 $\begin{tabular}{ll} Table \ IV \\ \ \ & \mbox{Kinetic parameters for squamous cell} \\ \ \ & \mbox{Carcinoma of Larynx} \\ \end{tabular}$ 

 $(t_a = 20 \text{ hr.})$ 

LI  $T_{exp}$  $T_{\rm int}$ Sex/Age (per  $T_{lin}$ (hr.) cent) M/49 yr. 5.I 392.0 315.2 254.4 M/52 yr. 6.4 308.8 233.6 214.4 F/54 yr. 0.6\* 3,326.4 2,664.0 2,160.0 M/55 yr. 4.6 432.0 347.2 281,2 M/59 yr. 6.3 316.8 254.4 206.4 F/62 yr. 6.9 289.6 232.0 188.8 M/62 yr. 6.2 321.6 241.6 222.4 F/64 yr. 252.8 233.6 337.6 5.9 M/66 yr. 7.1 278.4 211.2 193.6 M/66 yr. 1.0 1,996.8 1,596.8 1,291.2 M/67 yr. 3.5 571.2 457.6 371.2 M/71 yr. 275.2 219.2 179.2  $7 \cdot 3$ 

<sup>†</sup> Possibly malignant.

<sup>\*</sup> Post irradiation.

entiated forms and ultimately enter a functional compartment or die. This scheme defines a minimum 3 compartment system in which cell compartment size and population level are maintained and regulated by external and internal feedback control mechanisms.

Within the proliferative compartment, internal regulatory controls further compartmentalize the proliferating cell cycle into at least 4 well-defined phases: the pre-DNA synthesis (G<sub>1</sub>) phase; the DNA synthesis (S) phase; the post-DNA synthesis (G<sub>2</sub>) phase; and the mitosis (M) phase<sup>12,13,20</sup> (Fig. 4). Mammalian tissues are usually more complex, and may contain a population of potentially proliferative G<sub>0</sub> cells which may divide at a very low rate or only on stimulation to enter the cell cycle. As this compartmentalized scheme relates to the cell renewal system, additional classes of differentiating, maturing and functional cells yield a basic model of more than 3 and frequently at least 6 compartments.<sup>20</sup> Normally, cell division follows the G2 period and cells proceed through the cell cycle within a few hours of completing DNA synthesis. In most mammalian cell systems thus far studied,  $T_s$  is  $\sim 6$  to 10 hours;  $t_{g_2}$ ,  $\sim$ 2 to 3 hours;  $t_m \sim 1$  hour; and  $t_{g_1}$  varies widely, from minutes to months, and is primarily responsible for the variation in t<sub>e</sub> among different tissues.<sup>17</sup> The cell cycle times appear to be shorter in certain cells of the adult mammal than in some of the fastest growing experimental tumors.15 Neoplastic growth, therefore, involves kinetic parameters other than only the proliferation rate, as for example, the growth fraction; i.e., the fraction of cells participating in the proliferative pool,16 and the extent of cell loss through death and migration, 15,21

#### ANALYSIS OF KINETIC PARAMETERS

Providing the proliferating system is in a steady state of cell renewal, and the distribution of t<sub>e</sub> is invariant, then the number of cells in DNA synthesis in the proliferating population is proportional to the

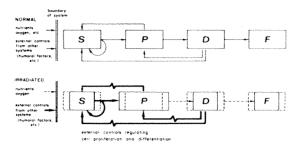


Fig. 3. Proliferating cell system represented by classes of cells with specific attributes of proliferation (P), differentiation (D), and function (F). Stem cells (S) are self-maintaining and provide progeny for the proliferating population. The lower scheme illustrates possible radiation effects on cell proliferation kinetics.

time spent in the S period, and  $N_s/N = t_s/t_c$ , where  $N_s/N = LI$ , the TdR-H³ labeling index. If  $t_s$  is known, then the important information of  $t_c$  can be determined from the labeling index. The TdR labeling index, therefore, is a valuable parameter, since it provides information on the growth characteristics of the tissue; viz., the sites of cell proliferation, and the rates of cell proliferation.

The average time taken for the cell number in a population to double, i.e., the tissue doubling time, is usually longer than the cell cycle time;  $T > t_c$ . When all cells in a population are proliferating, and the rate of cell birth equals the rate of cell loss by death or emigration, the population is in a steady-state of cell renewal; the growth rate is *linear* and the rate of cell proliferation is constant. The fraction of cells dividing per hour is dN/dt = k, where t is the mean transit time through the compartment. Since in the steady-state system, the cell influx equals the cell efflux, and there is the same number of cells in each generation, then when all cells are proliferating,  $k_i = k_j$  and  $k_{ij} = k$  and dN/dt = kN. Integrating,  $N = N_0 e^{kt}$ , where  $N_0$  is the cell number at time t = 0. In *linear* growth conditions,  $N/N_0=1$  and the growth rate constant, k = 1. If  $t_c$  is invariant, then  $k = t_c/$  $T_{lin}$ , where  $T_{lin}$  is the tissue doubling time assuming linear growth rate characteristics. Since LI =  $t_s/t_c$ , then  $t_c = T_{lin} = t_s/LI$ . This relationship is described as the rectangular phase distribution, in which all cells are proliferating,  $k_{ij} = k$ ,  $t_c = T$  and N is the same in each generation; this would obtain in steady-state cell renewal systems.

When all cells are dividing with an invariant t<sub>e</sub> and there is no cell loss from the proliferative compartment, the growth rate is exponential. Here,  $k_i = 0$  and dN/dt=  $k_i N$ ; integrating,  $N = N_0 e^{k_i t}$ , where  $k_i =$ 2/T. In this system, the population doubles with each generation, and growth rate is equal to the labeling rate, so that dN/dt = $LI \cdot N/t_s$  and  $LI = In 2 \cdot t_s/t_c$ . Under these conditions,  $t_c = T_{exp} = 1n \ 2 \cdot t_s / LI$ , and a growth rate constant of proportionality,  $\lambda$ , is introduced.  $\lambda$  is dependent on the position and duration of the S period in the cell cycle; it will lie between 2 ln 2 and ln 2 for the extreme case of exponential growth. This relationship is described as the exponential phase distribution for an idealized distribution of cells growing in log phase, te is invariant, ki=0 and N doubles with each generation. Such ideal exponential growth rates are rarely found in mammalian systems; this type may represent the extreme case of neoplastic growth—possibly lymphoma or early metastatic growth in lymph nodes—where control mechanisms no longer limit cell proliferation, and the population doubles with each generation.

Proliferating cell populations in vivo are not in an ideal steady-state of cell renewal nor in exponential growth; they have growth rates characteristic of the particular tissue. Real systems do not necessarily have constant growth rates, and  $\lambda$  must be determined from the phase distribution diagram for each proliferating cell system. In the case of tumors, for example, assuming an exponential cell birth rate, cells may be lost from the system at a variable rate of exfoliation, metastases and death. If it is assumed that these cell loss factors are constant, and  $k_i > k_j$ , then with an exponential cell birth rate, the growth rate dN/dt = $(k_i-k_i)N$ . The result is a growth rate intermediate between a linear and exponential rate, and while  $k_i = \ln 2/t_c$ , but  $k_i - k_i =$ 

In  $2/T_{\rm lin}$ . The value of  $T_{\rm int}$  for tumors, therefore, depends to a large degree on the relative values of  $k_i$  and  $k_j$ , and the extent to which  $k_i > k_j$ . For most experimental mammalian tumors,  $\ln 2 \le (k_i - k_j) \le 1.0$ , and  $(k_i - k_j)$  is of the order of 0.75, so that generally,  $T_{\rm int} = 0.75$  t<sub>s</sub>/LI. This relationship is defined as the *intermediate phase distribution* in which the cell system is expanding,  $\lambda > \ln 2$ , and the shape of the curve is influenced by the *cell loss factor*.

The equations for these models are based on a knowledge of 3 parameters: the growth rate constant; TdR labeling index; and the duration of DNA synthesis. The growth factor  $\lambda$  can be determined from the cell phase distribution;  $\lambda = T \cdot LI/t_s$ .  $\lambda$ therefore corrects for the lack of proportionality between the fraction of cells in the S phase and the duration of that phase, and thus depends on the position and duration of the S phase within the cell cycle. With only the values of TdR-H<sup>3</sup> labeling indices now available, an accurate measurement of the duration of DNA synthesis in human tissues presents some difficulties. For the determination of the duration of the S period alone, the use of double-labeling with two DNA precursors adapted to the *in vitro* technique is attractive. 19,24 The method involves pulse-labeling the proliferating population first with TdR-H3, then waiting for a period equal to or less than t<sub>g2</sub>, and pulse-labeling again with TdR-C14. During the interval between labels, cells labeled only with H<sup>3</sup> pass out of DNA synthesis, and these will be proportional in number (N<sub>H</sub><sup>3</sup>) to the time (t), between labels. Cells labeled with C14 were in DNA synthesis, and these are proportional in number (Nc14) to the duration of the S phase. Using autoradiographic methods capable of distinguishing between the two labels, the  $t_s = N_c^{14} \cdot t/N_H^3$ . The values for T in Tables 1 to 1v are based on kinetic analysis of observed pulse-labeled TdR-H<sup>3</sup> labeling indices in the tissues, together with the t, values in the range of those found in the different human cell populations in the 13 patients examined in Table

v; i.e., ts values of 12.5 hours, 12.5 hours, 15 hours, and 20 hours for normal and inflammatory tissues, and benign and malignant neoplasms, respectively. Recently, several normal patients and patients with leukemia, neoplastic effusions and solid neoplasms have been studied in a number of clinical laboratories using more complex serial sampling techniques after TdR-H3 labeling in vivo. The human data indicate S period values in some normal tissues and leukemic blast cells of ~10 to 15 hours, and in neoplastic tissues,  $\sim$ 20 to 30 hours. 11,18 These values compare favorably with those determined with the *in vitro* doublelabeling method. Further, cell generation times are much longer in man than in laboratory animals, and all phases of the cell cycle appear to be affected in the change in cell generation times, indicating altered rates of biochemical events concerned with the different phases of the cell cycle.

#### DOUBLING TIMES IN HUMAN TISSUES

Provided that the spread of t<sub>c</sub> in the proliferating population is not great, T is proportional to  $N_c$  and N; i.e.,  $I/T = N_c/N$ . If the fraction of cells entering mitosis each hour is known, then  $T = N/mN_c$ , where m is the mitotic rate. If t<sub>s</sub> is known with some precision, the  $N_s/N = (t_s \cdot mN_c)/N$  and  $LI = (t_s \cdot mN_c)/N$ . If all cells divide,  $t_c = T$ and  $T = t_s/LI$ .<sup>22</sup> The more realistic situation in vivo is one in which the cell population is expanding, the proliferating cells have a spread in cell cycle times, and a population of nonproliferating cells are also produced. However, provided the cell phase distribution is known-whether the structure of such a distribution can be determined with any accuracy is a measure of the extent of our understanding of a particular cell population-and t<sub>s</sub> can be estimated with some precision, then the growth rate of T of a given cell population, such as a tumor, can be determined from a knowledge of the TdR-H3 labeling indices. This determination may be used for predicting T in human tissues only if all cells proliferating are labeled, and there is no cell loss by

 $T_{ABLE}\ V$  Kinetic parameters for human tissues  $using\ double\ labeling\ method^5$ 

Sex/Age	Sex/Age Tissue		t <sub>s</sub> (hr.)	T (hr.)
M/ <sub>47</sub> yr.	Trachea,			
	normal	2.9	13.0	448.3
$M/_{53}$ yr.	Carina,			
	normal	1.8	12.0	666.7
M/52 yr.	Bronchus,			
	normal	5.1	11.2	219.6
M/66 yr.	Bronchus,			
	normal	4.6	11.5	250.0
M/8 yr.	Larynx,			-
	papilloma	10.4	15.6	120.0
F/12 yr.	Larynx,			
	papilloma	10.1	16.9	133.1
F/37 yr.	Larynx,			
	papilloma	5.6	11.6	168.2
M/61 yr.	Larynx,			
	carcinoma	7.7	22.1	204.5
M/69 yr.	Larynx,		A. A. C.	
	carcinoma	6.8	18.8	214.8
M/66 yr.	Bronchus,			
	carcinoma	6.3	20.9	260.6
M/72 yr.	Bronchus,			
	carcinoma	8.9	23.3	196.4
$M/_{59}$ yr.	Esophagus,			
	carcinoma	7.9	25.4	250.7
M/64 yr.	Esophagus,			
	carcinoma	7.3	22.0	235.0

emigration, differentiation or death. Thus far, only limited information is available on the accurate quantitative estimation of cell loss—in solid tumors, e.g., by exfoliation, metastases, and death—and thus, tissue doubling times and turnover rates determined from these models are, at best, only approximate, and represent potential tissue doubling times.<sup>21</sup>

#### CELL LOSS

The rate of cell loss from a proliferating population is an important parameter defining the growth characteristics of the population. In the steady-state renewal system with linear growth characteristics, such as the epithelium of the small intestine or the bone marrow, the rapid turnover times of I to 2 days ensure maintenance of tissue homestatic control mechanisms for contin-

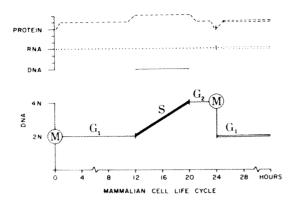


Fig. 4. Mammalian cell cycle in relation to nucleic acid and protein synthesis *in vivo*. The cell cycle shown lasts 24 hours; protein and RNA synthesis occur throughout the cell cycle, whereas DNA is synthesized only during a defined period (S) during interphase (see text).

uous cell replacement for cell loss by normal processes of differentiation, emigration and physiologic attrition. The value of the labeling index as a kinetic parameter for estimation of the tissue turnover time, therefore, would depend to a large degree on the extent of cell loss. In neoplastic tissues, on the other hand, cellular control mechanisms which maintain population size and regulate cell turnover, may no longer be effective, and the rate of cell loss may very well be the important determining factor in the measurement of tissue doubling times. In the human tissues examined in the present study, this was readily evident in the juvenile squamous cell papillomas (Table III). Here cells were infrequently labeled and left the proliferating compartment after division but did not emigrate, and the cell loss factor was negligible. The contact ulcer squamous granuloma listed in Table II, on the other hand, had an extremely short turnover time, but the rate of cell loss by exfoliation and death was marked. The tissue growth rates of papillomas were much greater than the inflammatory ulcer granulomas, but this was not the case for the cell proliferation rate. Thus, the growth rates of these different tissues were largely determined not only by the proliferative capacity, but rather by the rate of cell loss.

#### GROWTH FRACTION

The fraction of cells proliferating  $(N_p)$  in the entire cell population (N), i.e., the growth fraction (G.F.)16 is a third important kinetic parameter in the study of tumor growth; G.F. =  $N_p/N$ . The estimation of the growth fraction in experimental or human tumors cannot be made by a single labeling method, and more complex labeling and serial sampling techniques are required. The concept of the growth fraction involves two classes of cells (one proliferating and one nonproliferating), and these comprise the tumor cell population. The extent to which cells may move between the two compartments is not as yet understood. Further, the concept signals the importance of slowly or nonproliferating cells in tumors, particularly in regard to the therapy of clinical cancer, but much work is required.

#### RNA SYNTHESIS IN HUMAN TISSUES

The methods for analysis of cell population kinetics for characterizing the proliferate state of a growing tissue are primarily related to DNA synthesis in individual cells. The biochemical regulation of the events which occur during cell proliferation and differentiation is not necessarily limited to DNA synthesis for cell reproduction. Cell proliferation kinetics are concerned with the control of DNA synthesis and cell division, and thus involve at least 3 main biochemical processes during the cell cycle: DNA synthesis; RNA synthesis; and protein synthesis, particularly enzyme and nucleic acid precursor synthesis (Fig. 4).1,2 We have been examining RNA synthesis in human tissue biopsy specimens from the pharvnx, larvnx and adjacent structures, by a technique which adapts to the in vitro hyperbaric oxygen method described for the incorporation of UR-H3 and other labeled RNA precursors. Here, too, the in vitro experimental conditions are controlled in order that the cellular labeling occurs in cells which were synthesizing RNA in the patient.

In the normal mucosal epithelium, autoradiographic studies have revealed that within 2 or 3 cell layers which comprise the

proliferating population, there is very active RNA synthesis occurring in the nucleus, and later the label appears in the cytoplasm in all interphase cells. In addition, nucleolar RNA synthesis is pronounced soon after the onset of incubation of the tissue. However, as cells leave the germinal zone and thus the proliferating cell population, they become more differentiated, and subsequently show signs of nuclear degeneration, hyalinization and keratinization. RNA synthesis ceases abruptly. In some normal tissue autoradiographs examined from clinical patients, these biochemical transformations may occur with 1 to 2 cell layers removed from the proliferative zone, and no RNA synthesis is occurring in interphase nuclei, nor is there evidence of label appearing in the cytoplasm. Thus, in the normal human mucosal epithelium studied, the rate of nuclear RNA synthesis is roughly constant during the cell cycle of the proliferating population, except during cell division; here RNA synthesis slows or ceases, and this is particularly apparent during metaphase and early anaphase in mitotic cells.23,24

Studies of biopsy specimens from 18 patients with inflammatory and neoplastic diseases of the larynx and hypopharynx have demonstrated that nuclear RNA synthesis may be markedly perturbed when cells do not undergo normal patterns of degeneration, but have left the proliferative zone. In inflammatory lesions, there is an increase in nuclear, and particularly nucleolar labeling with UR-H3, and this is especially apparent in areas where acute and chronic inflammatory cell infiltration (both polymorphonuclear leukocytes and small round cells) has occurred. Increased label appears in the cytoplasm with prolonged incubation. In cells distant from the proliferative zone, RNA synthesis decreases, and in relatively normal tissue regions, activity ceases as the cells leave the proliferating region. In neoplastic tissues, on the other hand, increased nuclear labeling is not as apparent as in the case of inflammatory tissues. However, in tumor tissues, nuclear RNA synthesis is occurring

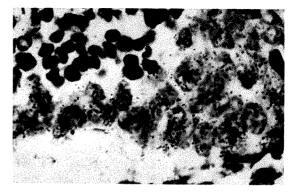


Fig. 5. Autoradiograph of a slowly proliferating laryngeal cord polyp in a 49 year old man. Nuclear RNA synthesis persists in cells which have not undergone normal degenerative changes but have moved out of the proliferative zone (see text; 1,800 ×; H and E; UR-H³).

in cells quite distant from the germinal cell layer, but not necessarily at a greater rate than normal cells. In such tissues as laryngeal cord polyps, nucleic acid synthesis decreases and finally ceases as the highly differentiated and degenerative changes in the tissue develop (Fig. 5).

#### DISCUSSION

Thorough analysis of cell population kinetics in human tissues in vivo is precluded, primarily by limitations imposed by experiments in man. Recent studies on cell proliferation kinetics in patients with acute leukemia and widespread terminal malignancies indicate that valuable information on cellular proliferation may be obtained from peripheral blood, bone marrow, leukemic cells and neoplastic effusions. 20,21 These neoplastic tissues are primarily cell suspensions, rather than solid tumors, and hence permit the use of techniques which involve multiple sampling procedures. Further, such cell populations are not necessarily anoxic, and therefore, the availability, incorporation and utilization of labeled nucleic acid precursors, and particularly TdR-H3, can apparently occur without increasing the oxygen concentration of the tissue.

While there is a considerable amount of quantitative information on the *in vitro* incorporation of TdR-H<sup>3</sup> in human neoplasms, many of these studies are limited,

in part, by the considerable variation in labeling between and within different tissues, and particularly solid tissues, of sites of cellular proliferation, the sizes of the proliferating populations, and the rates of cell division. The introduction of a safe and reliable in vitro method for analysis of cell kinetics in human tissues should provide valuable information for a better understanding of the growth rates of human tissues in vivo. The present report evaluates a method for the incorporation of labeled nucleic acid precursors into surgical and biopsy specimens in vitro—primarily TdR-H3, TdR-C14 and UR-H3. The techniques provide kinetic information on: (1) percentage labeling indices and DNA synthesis times in normal and diseased human tissues: and (2) proliferative capacities of these tissues. These data permit prediction of tissue doubling times in human tissues. However, the method provides no information on cell loss, e.g., by death, differentiation or emigration, and thus the information is limited to the determination of potential tissue doubling times only. There is now only very little information on quantitative methods for estimating cell loss in human tissues. Studies on cell loss from experimental tumors21 indicate that reliable quantitative data are lacking and difficult to obtain by cell kinetic labeling techniques presently available. Limited information is recently available on changes in the proliferating and nonproliferating fractions of blast cells in acute leukemia.11,18 This information is very important, particularly in regard to cellular control mechanisms and cancer, and it would be extremely valuable for the estimation of growth rates, and thus tissue doubling times, in solid tumors in man. Thus far, there are few reliable methods for the accurate determination of cell loss in tumors, e.g., by exfoliation, metastases, and death. Therefore, until improved techniques become available, estimates of tumor doubling times in vivo are not precise, and under ideal conditions of cell population growth, are at best potential doubling times. Based on DNA labeling studies, both pulse-label-

ing and double-labeling, together with RNA labeling experiments previously reported. 5-10 we have now shown that labeling indices and DNA synthesis periods in over 200 human biopsy specimens of normal and diseased tissues vary widely even when uniform labeling occurs, and therefore tissue doubling times vary widely as well. Hence, in spite of similar morphologic or pathologic classifications of many of these cell populations, growth rates of human tissues in vivo can vary widely depending on the proliferative capacities of the tissues, the proportion of proliferating and nonproliferating cell populations, and the extent of cell loss.

#### CONCLUSIONS

Much more work needs to be done on cell population kinetics in human tissues for a better understanding of the growth characteristics of normal and diseased, and particularly neoplastic, tissues in man. It is becoming increasingly important to know more about cell growth and cell division in human tumors, and thus cellular regulatory mechanisms concerned with control of cell proliferation in clinical neoplasia.1,2,7,11,18 As more quantitative data on the kinetic analysis of human tumor cell populations become available, a greater understanding of the factors contributing to the over-all growth characteristics of clinical neoplasia will become available. Information is required on how rapidly individual cells proliferate in human tumors and whether they proliferate faster or slower, in terms of distribution of cell cycle times, than cells in adjacent premalignant tissues, or in the normal tissues of origin. Further, therapeutic experience has demonstrated the significance of metastatic disease in the control of clinical cancer in man, and information is required on cellular proliferation in metastatic as well as in primary neoplasms. Such studies on cell population kinetics and oncology are essential for the understanding of cellular control mechanisms and cancer. Eventually, this information will provide a better insight into the selection of methods for the prevention and detection of neoplastic disease, for improvement of therapeutic modalities, and ultimately the prediction of recurrence, and thus, prognosis, in each patient presenting with clinical cancer.

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#### A TEACHING CARREL FOR USE IN RADIOLOGY\*

By BRUCE DOUST, M.B., and HARRY W. FISCHER, M.D. ELOISE, MICHIGAN

IN RECENT years, the demand for medical manpower has increased rapidly, so that a widespread and well-recognized shortage of physicians now exists. <sup>2,3</sup> Various estimates of the rate of increase in Radiologists' work load have been made. Film utilization provides a crude estimate of work load. At the Wayne County General Hospital this has, in recent years, grown at approximately 8 per cent per annum (Fig. 1).

When an attempt is made to allow for the increase in professional effort that this represents, the growth rate is much higher, due to the increase in the proportion of complex procedures. Annual growth rates of activity as high as 30 per cent have been estimated. In line with this, it has been estimated that the number of radiologists required in the U.S.A. by 1975 will be between 20,000 and 25,000 or roughly 3 times the number available in 1966. Clearly, the work load on individual radiologists is likely to increase.

In order to mitigate the effect of this increase, efforts must be made to increase the efficiency of individual radiologists. Therefore, we are looking into ways of increasing the efficiency of teaching methods. As a first step we have investigated the currently available teaching carrels, with the aim of selecting the one most suitable for the teaching of radiologic subjects.

The criteria on which selection was based were:

The machine should produce a high quality image, as nearly the same as the original radiograph as possible.

The price for a working system should be low.

As we wish to do experimental work on

the effects of the form of the instructional program on the learning process, a system with the greatest possible flexibility of program format is required.

The system should provide for active student participation in the program and there should be some way of obtaining an objective assessment of student performance.

# DESCRIPTION OF THE TEACHING CARREL

Specifications. The carrel has the following specifications: total height, about 50 inches; depth, about 30 inches; width, about 40 inches; imaging system, 35 mm. black and white slides projected by a projector with 3 inch lens\* on a plastic screen, via a single mirror.

Sound System. A cassette tape player† using standard tape cassettes is employed.

Student Response System. Both the cassette tape player and the responder can trigger the projector to change slides. ‡

- \* Kodak Carousel Projector.
- † Norelco Synchroplayer.
- ‡ Dymedia Responder, Dymedia Inc., 2450 El Camino Real, Palo Alto, California 94306.

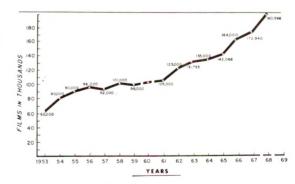


Fig. 1. Growth of film utilization at Wayne County General Hospital from 1953 to 1969.

<sup>\*</sup> Presented at the Eighteenth Annual Meeting of the Association of University Radiologists, Lexington, Kentucky, April 29-May 1, 1970.

From the Department of Radiology, Wayne County General Hospital, Eloise, Michigan and the University of Michigan, Ann Arbor, Michigan.

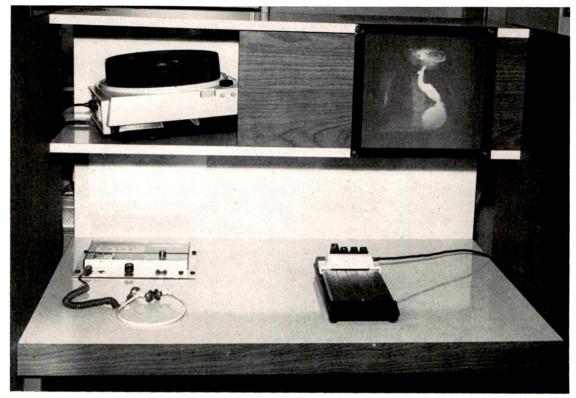


Fig. 2. Over-all view of the teaching carrel. The cassette tape player is to the left, the responder to the right. The projector is on a shelf above the desk level. The display screen is to the right.

Figure 2 is an over-all view of the carrel. The projector system is situated above the level of the bench allowing greater working space to the student with a compact carrel. The screen is roughly at eye level, approximating the position of films on a viewbox. A centrally placed screen would be more realistic, but would introduce problems with the projection system, which is at present very simple.

The Synchroplayer is screwed into the left side of the bench top. This unit will not record. It will play cassettes which must be recorded on a separate unit; it is not possible for the student to erase or to alter the tape. Earphones are necessary, not only to avoid disturbing other students, but also to exclude the considerable noise from the projector cooling fan. The responder is to the right of the recorder.

A single switch, (not shown on the picture) should be incorporated, so that all the

components of the carrel can be turned on simultaneously, thereby simplifying operation of the carrel.

The Responder. This device allows the student to respond to questions posed by the program. The 4 buttons represent alternative answers to a question. Only when the correct button is pressed does the projector change to the next slide. This gives the student the correct answer instantly. Figure 3 shows the interior of the responder. It contains a standard computer punch card. This is punched whenever any of the buttons is pressed, thus recording the student's mistakes as well as his correct answers, and makes the data available for computer processing if required. Several alternative programs of correct answers are available within the responder.

#### THE PROGRAM

The programs are recorded on standard

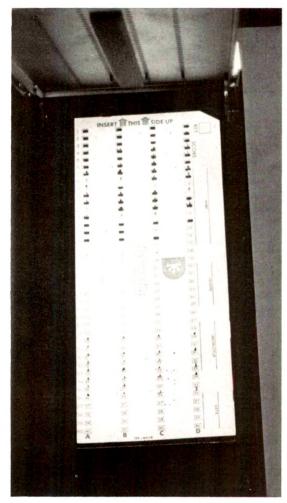


Fig. 3. The interior of the responder showing punch card in position.

stereo tape cassettes, using a specially modified stereo tape recorder. The commentary is recorded on one of the two stereo tracks. On the other track are recorded pulses which trigger the projector to change slides. There is no restriction on the time interval that may elapse between one slide and the next, so that the length of commentary for any one slide may be as short or as long as required. This degree of flexibility is not available in certain other commercial systems. Thus, the projector can be triggered by either a pulse from the recorded program, or a correct response from the student.

Figure 4 is a block diagram of a typical program. Each teaching slide change is

triggered by a pulse from the recorder. A question slide, however, requires a student response to trigger progression of the program. It also illustrates a limitation of the system. There is no provision for stopping the tape during the time the student is considering his answer. Thus, a silent gap must be left in the tape commentary. This will be unduly long for some students, and not long enough for others. Further, if the student fails to respond, the tape and slides will be out of step.

#### ADVANTAGES

- (1) The carrel is available to students at any time, night or day.
- (2) Unlike other simple carrel setups this system allows student response.
- (3) The quality of the image produced is good, much better than that available with cine film or TV displays.
- (4) Because student response is possible, programs can be constructed to cultivate judgment, as well as to teach fact.
- (5) The time between slide changes is widely variable—a feature not available in some other commercially available audiovisual devices.
  - (6) Film handling is eliminated.
- (7) Components of the system are freely available commercially.
- (8) Programs can be prepared simply without special help from outside.

#### LIMITATIONS

(1) Programs which are branched, *i.e.*, provide alternative instruction paths de-

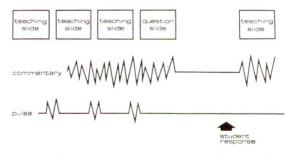


Fig. 4. Diagrammatic representation of a teaching program requiring student response. Peaks in the lower track represent recorded pulses which trigger slide changes. (Further description in text.)

pending on the student response, cannot be used with this carrel.

- (2) As the speed of the taped commentary is constant, the student cannot vary the program speed to his own preference.
- (3) The radiographic image is not quite the same as the original radiograph, being smaller and brighter.
- (4) Student acceptance of carrel teaching varies. Some students will not use the system at all. There is some evidence that male students, students with language difficulties, and slow students prefer the carrel to a lecture.<sup>4</sup>
- (5) Some subjects are not suitable for programming onto a carrel. It cannot replace (but may supplement) practical experience of techniques, e.g., fluoroscopy for barium studies. Also, subjects requiring an understanding of dynamic phenomena cannot be taught on this carrel. Such subjects require the use of cine or TV.
- (6) The carrel cannot answer students' questions.

#### CONCLUSIONS

A simple, inexpensive carrel system suitable for displaying radiographic images,

and allowing student response, is presented.
Its advantages and limitations are discussed.

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# ANGIOGRAPHIC APPEARANCE OF THE CANINE KIDNEY IN ACUTE HEMORRHAGIC SHOCK—MODIFICATION BY SALINE INFUSION, THAM INFUSION, AND REINFUSION OF BLOOD\*

By MILTON ELKIN, M.D., CHIEN-HSING MENG, M.D., and LOUIS MENDEZ BRONX, NEW YORK

THE blood vessels of the kidney might be expected to show varying responses to acute hemorrhagic shock. Because of the decrease in blood volume there could be shrinking of all vascular beds including the renal. On the other hand, the fall in systemic blood pressure could be compensated by diminution of the renal vascular resistance in order to maintain adequate renal blood flow, which would be evidenced angiographically by a dilatation of the renal vessels. Brake et al.<sup>2</sup> studied the response of the in situ denervated kidney to periods of partial and total renal artery occlusion in the anesthetized dog; with a reduction in renal artery pressure to 40 to 50 per cent of control level or lower, there was a decrease in renal vascular resistance during the period of partial occlusion. The average renal artery pressure during the occlusion was 55 mm. Hg. Following release of the obstruction there was a marked increase in renal vascular resistance. Ritter<sup>13</sup> had reported that with fall in systemic blood pressure, renal resistance decreases to a minimum at approximately 65 mm. Hg and remains constant despite further blood pressure fall. The diminished resistance was attributed chiefly to changes in caliber of the afferent glomerular vessels. Tirka et al.8 using the thermodilution catheter in a renal vein of dogs reported that in hemorrhagic hypotension most experiments showed a rise of the renal fraction of cardiac output, indicating relatively less resistance to blood flow in the kidney than in other organs under conditions of hypovolemic hypotension.

Selkurt,<sup>14</sup> using direct renal blood flow measurements, found that in the dog acute hemorrhagic shock was accompanied by increased renal vascular resistance with diversion of proportionately greater shares of blood to other parts of the body. He reported that there is a closure of the renal cortical circulation with some persistence of the medullary circulation and described this as a redistribution of regional circulation rather than the opening up of new pathways of circulation in the medulla. 15 On the other hand, Aukland and Wolgast<sup>1</sup> stated that acute hemorrhage in the anesthetized dog, to a mean arterial pressure of 50-65 mm. Hg, reduced cortical and medullary blood flow to the same extent. They concluded that hemorrhagic hypotension in dogs leads to a progressive and fairly uniform rise in renal vascular resistance, without any selective hemodynamic response in the juxtamedullary circulation. Lauson et al.11 reported that hemorrhagic shock in man was associated with diminished renal blood flow and increased renal vascular resistance (afferent arteriolar constriction).

Kupic and Abrams<sup>10</sup> studied the acute and delayed renal vascular changes in dogs subjected to hemorrhagic hypotension to levels of 50 and 30 mm. Hg mean blood pressure. Analysis of serial angiograms demonstrated a decrease in the size of the main renal artery and of the segmental branches, slowing of renal circulation time, irregular cortical nephrogram, and decrease in size of the renal vein. With a mean arterial pressure below 35 mm. Hg, the outer renal cor-

<sup>\*</sup> From the Department of Radiology, Albert Einstein College of Medicine, Bronx, New York. Supported by U.S.P.H.S. Research Grant N.I.H. GM 15809.

tex was poorly perfused with maintenance of perfusion of the inner cortex and outer medullary regions.

Goetz et al.6 reported that the administration of tris (hydroxymethyl) amino methane (THAM) to dogs in hemorrhagic shock produced an immediate drop in renal vascular resistance with a corresponding rise in renal blood flow.

Kramer<sup>9</sup> reported an increase in renal vascular resistance in hemorrhagic shock, with persistence of the vasoconstriction after reinfusion of the blood. Selkurt<sup>14</sup> found that upon reinfusion of blood, there is an immediate, although not complete, restoration of renal blood flow and mean blood pressure to approximately 70 to 80 per cent of the control figures, with simultaneous decrease of the renal vascular resistance to approximately the control value.

The purpose of this paper is to report observations in dogs on angiographic changes produced by acute hemorrhagic shock, acute hemorrhagic shock followed by saline infusion and acute hemorrhagic shock followed by THAM infusion as well as on the angiographic appearance following reinfusion of the blood.

#### METHOD

As described previously,5 selective renal angiography was done on dogs using thorotrast as the contrast medium. A red Kifa catheter was inserted into the renal artery under fluoroscopic control by the Seldinger technique with percutaneous puncture of a femoral artery. In order to reproduce injection and timing factors in serial angiography, an automatic injector (Cordis) was used, which not only injected the same amount of thorotrast each time at the same rate, but also initiated the roentgenographic exposure at the same time in the course of the injection. The dose of thorotrast was 0.2 or 0.3 ml. per kg. of body weight. Several of the experiments were done with direct magnification ( $\times 2$ ) using an x-ray tube with high speed rotating anode and an effective focal spot of 0.3 mm. (Dynamax 61). In some of the studies, films were exposed at the rate of 2 per second for a total

of 5 or 6 seconds; in other studies exposures were I per second or sometimes 2 per 3 seconds for a total of 5 to 8 seconds. Blood pressure was recorded continuously from a catheter in the lower aorta. In all experiments the dogs were anesthetized with sodium pentobarbital administered intravenously.

Acute hemorrhagic shock was produced by rapid bleeding from the femoral artery into a warmed graduated bottle containing heparin solution. When reinfused, the blood was passed through a fine metal filter to prevent the introduction of small clots. THAM, when given, was administered intravenously as a 0.3 molar solution in a dosage of 300 ml. in 30 to 40 minutes.

#### RESULTS

#### HEMORRHAGIC SHOCK

Acute hemorrhagic shock was produced in 14 dogs and a total of 30 angiographic studies were done in various stages of hypovolemic shock. Dog weights ranged from 12 kg. to 21 kg. In most experiments there was rapid bleeding of 500 to 750 ml., although in a few animals 1,000 ml. was bled. The range of bleeding was 18 to 59 ml. per kg. of body weight with the average 40 ml. per kg. Most bleedings were from 30 to 50 ml. per kg. Although most of the post-bleeding angiographic studies were done at mean systemic blood pressure of 40 to 60 mm. Hg, some were at levels as low as 20 to 30 mm. Hg. In most experiments angiographic study was done within 15 minutes of reaching the desired level of hypotension; additional follow-up studies were carried out at various periods after production of shock, usually at 30 and 60 minutes. The usual findings in acute hypovolemic shock were: (1) reduction in caliber of main renal, segmental, and interlobar arteries as well as of the intrarenal veins and the main renal vein; and (2) renal blood flow was diminished as judged by prolonged circulation time (slowing of the vascular phases) and increased reflux of the contrast medium from the renal artery into the aorta during injection for angiography (Table 1).

Table I

CHANGES WITH ACUTE HEMORRHAGIC SHOCK—
TOTAL OF 30 ANGIOGRAMS

	Increase	Decrease	Un- changed	Indeter- minate
Main renal				TO TO THE RESIDENCE OF THE PARTY OF THE PART
artery	4	25	I	
Segmental		_		
arteries	2	26	2	
Interlobar				
arteries	2	26	2	
Intrarenal				
veins		24	1	6
Main renal				
vein		23	I	6
Flow	Try and the same of the same o	29	I	

These results are similar to those reported previously.<sup>10</sup>

In most of the studies the over-all intensity of the nephrogram remained good. However, in 10 of the 14 dogs (18 of 29 angiograms) there was irregularity of the nephrogram suggesting intrarenal redistribution of blood flow away from the cortex (Fig. 1, A-C; 2, A and B; and 3, A-C), as reported by Kupic and Abrams. 10 However, the degree of nephrogram irregularity varied, its magnitude bearing no constant relationship to the level of the systemic blood pressure (Table 11). In our experiments angiographic evidence of poor cortical perfusion was seen at mean systemic pressures as high as 60 mm. Hg. In the 3 animals exhibiting nephrogram irregularity at mean systemic blood pressures above 50 mm. Hg, the hypotension had been present for 30 minutes or longer (30, 55 and 70 minutes); yet, the phenomenon of intrarenal blood flow redistribution in shock is not directly related to the degree of hypotension or to the duration of hypotension. In some animals with progressive lowering of blood pressure along with longer duration of the hypotension, the degree of nephrogram irregularity showed improvement. Thus in I dog there was marked nephrogram irregularity after 5 minutes of hypotension at a level of 42 mm. Hg; at 20

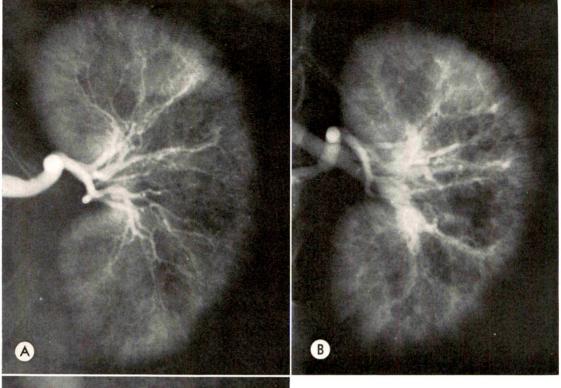
minutes with blood pressure 44 mm. Hg the irregularity was much less marked; at 50 minutes with blood pressure 46 mm. Hg the nephrogram was smooth. Such findings suggest the possibility that there is a changing pattern of intrarenal blood flow distribution despite the maintenance of a constant level of hypovolemic hypotension.

There has been a good deal of discussion in the literature about the Trueta shunt in shock. Unfortunately there is a lack of clarity in the criteria for the Trueta phenomenon. If the Trueta phenomenon is considered to be cortical ischemia resulting from redistribution of intrarenal blood flow, then this has been demonstrated by several investigators3,10,16 since the report by Trueta et al.17 This redistribution of intrarenal blood flow in the presence of hypovolemic hypotension supposedly results from vasoconstriction and increased resistance in the outer cortex with decreased resistance in the inner cortex and medulla.10 However, if the Trueta phenomenon is considered to be a true functional arteriovenous shunt with by-passing of the cortex and rapid circulation through the medulla or inner cortex, then one would expect to see rapid opacification of the renal vein; i.e., opacification earlier than occurs in the control angiogram. The demonstration of the opening of arteriovenous shunts in the dog kidney in hemorrhagic shock has been reported by Gömöri et al.7 in corrosion preparation studies. More and Duff12 did corrosion studies on 36 normal human

TABLE II

POOR CORTICAL PERFUSION AT VARIOUS
LEVELS OF HYPOTENSION

Systemic Mean Blood Pressure (mm. Hg)	Nephrogram Irregular	Nephrogram Smooth
20-29	2	
30-39	5	I
40-49	8	2
50-59	I	4
60-69	2	2
90-99		2



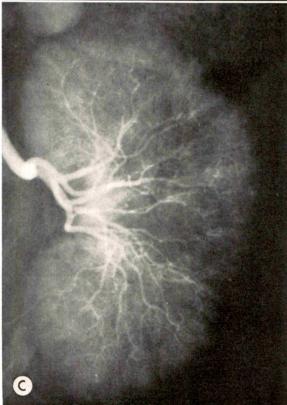


Fig. 1. (A) Control angiogram in 17 kg. dog; 2 second film after injection of thorotrast (magnification technique). Mean blood pressure is 153 mm. Hg and the urine flow 1.2 ml. per minute. There is no vein opacification. (B). Bled 1,000 ml. in 47 minutes, and in marked hypotension for 30 minutes. Mean blood pressure is now 21 mm. Hg; 2 second film. Main renal, segmental, and interlobar arteries are diminished in caliber. There is slight irregularity of the cortical nephrogram, although there is, in general, fairly good cortical perfusion despite the marked hypotension. There is good intrarenal and main vein opacification. Arcuate and interlobular veins are also visualized. The kidney is smaller than in A. There is marked diminution in the urine flow (few drops per minute). (C) Thirty-seven minutes after completion of rapid reinfusion of the blood; 2 second film. Mean blood pressure is 150 mm. Hg and urine flow 1.5-2 ml. per minute. There is no vein opacification. Kidney is back to control size.

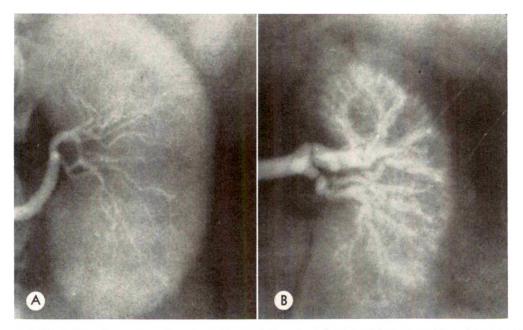
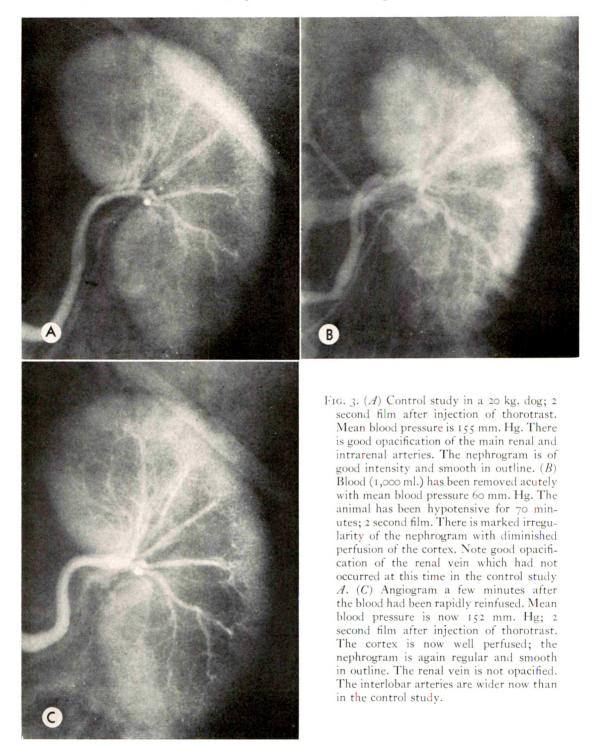


Fig. 2. (A) Control angiogram in 19 kg. dog; 1½ second film after injection of thorotrast. Mean blood pressure is 155 mm. Hg. The nephrogram is smooth with normal perfusion of the cortex. (B) Bled 750 ml. in 26 minutes with fall in mean blood pressure to 35 mm. Hg. The dog was in extremis, dying 10 minutes after this angiogram. There is marked dilatation of the main renal, segmental and interlobar arteries, possibly representing loss of vasoconstrictive tone in the moribund animal; yet, there is no opacification of cortical vessels.

autopsy kidneys; no true arteriovenous anastomoses could be demonstrated.

Trueta et al.17 stated that in the rabbit in several experimental situations, including hemorrhage, renal blood flow may be diverted from the cortex and make its intrarenal circuit through a medullary pathway. The by-passing channels are located in the deepest zones of the cortex and the subcortical zone of the medulla. As an indication of lowered resistance in this vascular by-pass, they reported that on direct observation of the exposed kidney during the period of cortical pallor they could see a pulsatile stream of intensely red blood in the renal vein. They suggested that the vasa recta serve as the chief conducting channels in the medullary by-pass associated with juxtamedullary glomeruli. They reported that blood passes more rapidly through this "lesser circulation" than it does through the kidney under normal circumstances. The medullary route includes: interlobular arteries, afferent arterioles of juxtamedullary glomeruli, efferent arterioles of these glomeruli and their derivative vasa recta to the interlobular veins. The cortical route includes: interlobular arteries, the afferent arterioles of the remaining glomeruli, efferent arterioles of these glomeruli and their derivative intertubular capillary network, and, finally, through the veins draining this network into the interlobular veins. Thus the channels of the medullary circuit are not arteriovenous anastomoses in the usual anatomic sense, but they have the physiologic significance of such anastomoses in that they allow the renal blood to flow in a low resistance circuit, by-passing functional elements of the kidney.

Daniel et al.<sup>4</sup> described a similar phenomenon in cats, dogs, monkeys and sheep. They also discussed the inconstancy of their experimental results and reinforced Trueta's earlier view that there may be intermittent alterations in the distribution of the intrarenal blood flow between the



cortical and medullary circulations.

Hence, Trueta and associates did not describe anatomic arteriovenous fistulas.

medullary by-pass could, on occasion, be of significantly lower resistance than normally and thus function as a physiologic shunt. However, they did indicate that the On such occasions the angiogram should

TABLE III

EFFECT OF SALINE INFUSION IN 7 EXPERIMENTS

	Abnormal in		No Change by	Toward	To Control in	
	Total	1		Saline in	Control in	10 Control in
Main renal artery	7		7	7		
Segmental arteries	6		6	6		
Interlobar arteries	7		7	7		
Flow	6		6	5		1*
Intrarenal veins	6		6	5	1*	
Renal vein	6		6	5	1*	

<sup>\*</sup> Dog with marked blood pressure rise after saline.

show early opacification of the main renal vein. This phenomenon of early vein filling was evident in 6 of our experimental animals (in 10 angiograms)—(Fig. 1, A-C; and 3, A-C). Although this early vein opacification might be interpreted as a functional shunt and be considered as evidence in favor of the Trueta phenomenon, a note of caution must be inserted. The early vein opacification could be a technical artifact. With hemorrhage, the kidney volume is decreased as is its blood volume. Also all arterial vessels diminish in caliber, including the main renal artery. Thus the early vein opacification might be related to injection factors; i.e., the narrowed renal artery ensheathing the catheter as compared to the freer position of the catheter in the control injection. It has been demonstrated that too wide a catheter with partial or complete block of the vessel will, in the normal condition, result in early vein opacification. That this may be the explanation is strengthened by the fact that in our hemorrhaged dogs early vein opacification has so far, in a few experiments, not been demonstrated by aortography or in selective angiography with use of a very narrow catheter.

In general the kidneys became smaller in size in hypovolemic hypotension as compared to the control size. With the unmagnified roentgenographic techniques used in these experiments the adult dog kidney measures about 4.4×7.5cm. Width

and length of each experimental kidney was measured and compared with control measurements. Arbitrarily a change of at least 5 mm. in either of these measurements was considered significant. In experiments with magnification roentgenography, a difference of at least 10 mm. was used as significant change. With this arbitrary yardstick 7 of 12 dogs in which accurate measurement could be made showed decrease in kidney size. In no case was the diminution in size great, averaging 6.8 mm. (unmagnified) and 13.5 mm. (magnified), with the largest change being 10 mm. (unmagnified) and 17 mm. (magnified).

### ACUTE HEMORRHAGIC SHOCK FOLLOWED BY SALINE INFUSION

In 7 dogs suffering from acute hemorrhagic shock, 500 ml. of isotonic saline was infused rapidly intravenously with angiographic study repeated within a few minutes after completion of the saline infusion. In 6 of the experiments the post-saline blood pressure showed no marked change from its pre-saline level. In 1 animal the pre-saline level of 44 mm. Hg rose to 113 mm. Hg after the saline; this result is unexplainable. After hemorrhage the angiograms showed the expected changes: diminution in size of the renal vessels, diminution of renal blood flow, and slight reduction in kidney size. Saline infusion produced no significant change in the appearance of the angiogram except in the I animal with the large increase in blood pressure during the saline infusion; in this dog renal blood flow returned to control appearance while main renal vein and intrarenal vein increased in size although not to their control appearance (Table III).

Three of these dogs showed irregularity of the nephrogram (redistribution of intrarenal blood flow) after hemorrhage; saline infusion effected no change in I (Fig. 4, A-C) and only minimal improvement in 2. Four dogs showed early main renal vein opacification after hemorrhage; after saline infusion 2 still showed the same degree of early vein filling and the other 2 slightly less.

In 6 dogs in which the kidney could be accurately measured none showed increase in renal size after the saline infusion as compared to the angiogram after hemorrhage.

# ACUTE HEMORRHAGIC SHOCK FOLLOWED BY THAM INFUSION

In 5 dogs suffering from acute hemorrhagic shock, THAM was administered intravenously (300 ml. 0.3 molar solution in 30 to 40 minutes) with angiographic studies repeated immediately and 30 minutes after the THAM infusion was completed. In 3 of the animals the main renal artery had diminished in caliber after hemorrhage; in all 3 the post-THAM angiograms showed increased size of the artery although in none did it reach control size. In all 5 dogs the segmental arteries were reduced in size; after THAM was administered 3 returned to control size, I toward control size, and I remained unchanged. In all 5 animals the post-hemorrhage angiograms suggested diminished renal blood flow; after THAM infusion 2 showed increased flow although not as good as the control, and the other 3 remained unchanged. In all 5 dogs the intrarenal veins had diminished in size; after THAM infusion 3 had returned toward control size and in the other 2 there was no change. The main renal vein had become

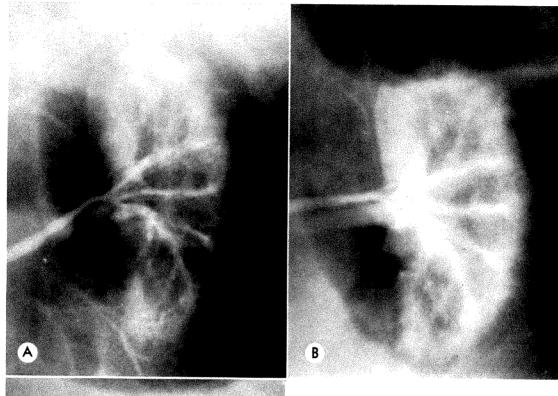
smaller in diameter in all 5 animals with hemorrhage; after THAM infusion all 5 showed return toward control size. All 5 dogs showed nephrogram irregularity after hemorrhage; in 2 dogs the post-THAM angiogram showed less irregularity (Fig. 5, A-E) and in the other 3 no changes. In these 5 dogs THAM infusion effected no significant change in kidney size.

The THAM infusion produced no significant change in the level of the hypotension

The THAM results are summarized in Table IV. As compared to saline infusion, THAM infusion does effect changes in the hypotensive angiogram with restitution of some of the abnormalities toward the control appearance. However, in no instance did the post-THAM angiogram, with maintenance of the hypotension, return to its control normotensive status.

## IMMEDIATE CHANGES AFTER REINFUSION OF BLOOD

In 10 dogs angiograms were obtained within a few minutes after rapid infusion of the blood, and comparison was made with the appearance of the angiogram made before hemorrhagic shock (i.e., control angiogram). In almost all animals reinfusion of the blood restored the blood pressure to its control level. The most usual findings were: increased size of the arteries (main, segmental and interlobar) (Fig. 6, A and B), diminution in caliber of the intrarenal veins, no change in size of the main renal vein and increased renal blood flow (Table v). In 5 dogs the angiogram obtained during acute hemorrhagic shock showed nephrogram irregularity (diminished cortical flow); in all 5 the angiogram after blood reinfusion demonstrated a smooth and homogeneous nephrogram. In 6 dogs the shock angiogram showed early opacification of the main renal vein; this was no longer present in any of these animals after blood reinfusion. In 10 dogs in which the kidney could be measured accurately, 4 showed an increase in renal size after blood reinfusion as compared to the control angiogram.



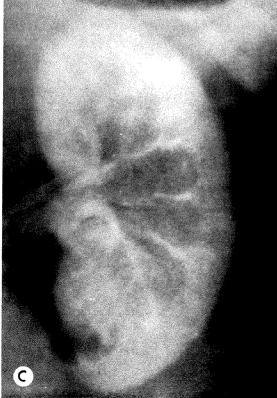
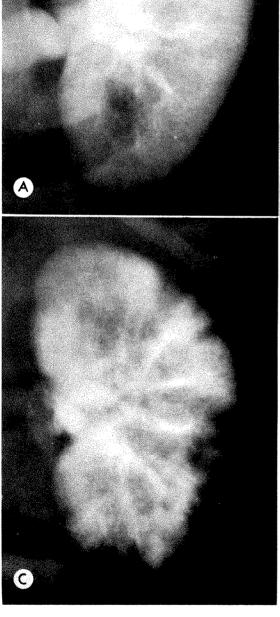


Fig. 4. (A) A 16 kg. dog had been bled 775 ml. Control mean blood pressure had been 117 mm. Hg, now is 43 mm. Hg. Hypotensive for 55 minutes. Control urine flow was 0.5 ml. per minute, now there is no urine flow; 21/2 second film after injection of thorotrast. There is marked irregularity of the nephrogram with markedly diminished cortical perfusion. The renal vein is opacified. (B) Angiogram 6 minutes after completion of infusion of 500 ml. of isotonic saline intravenously;  $2\frac{1}{2}$  second film. Mean blood pressure is 40 mm. Hg with still no urine flow. There is still diminished perfusion of the cortex and good opacification of the renal vein. (C) Angiogram 17 minutes after all blood rapidly reinfused; 2½ second film. Mean blood pressure is 124 mm. Hg with urine flow 2.6 to 4 ml. per minute. The nephrogram is smooth in outline with good cortical perfusion.



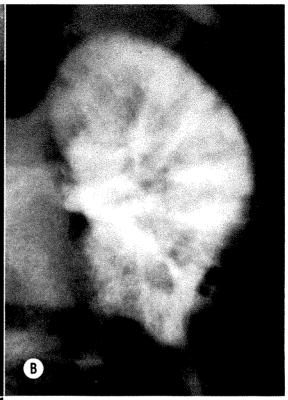


Fig. 5. (A) Control angiogram in 12 kg. dog; 2½ second film after injection of thorotrast. A small renal artery catheter was used in this experiment (PE 60). Mean blood pressure is 110 mm. Hg with a normal nephrogram. (B) Bled 650 ml. and in shock for 60 minutes; 2½ second film. Mean blood pressure is 23 mm. Hg. There is irregular perfusion of the cortex. (C) Angiogram immediately after completion of intravenous administration of 300 ml. of 0.3 molar THAM solution in 40 minutes; 2½ second film. Mean blood pressure is 28 mm. Hg. There is still irregular cortical perfusion, although slightly improved over B.

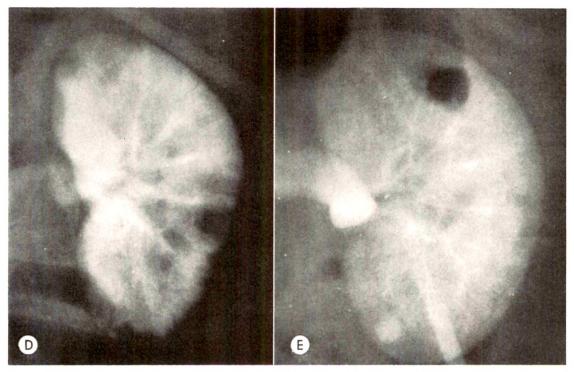


Fig. 5. (D) Angiogram 30 minutes after C;  $2\frac{1}{2}$  second film. Mean blood pressure is 28 mm. Hg. Cortical perfusion shows some further improvement, although it is still irregular. (E) Four minutes after completion of rapid reinfusion of blood;  $2\frac{1}{2}$  second film. Mean blood pressure is 114 mm. Hg. The nephrogram has returned to normal appearance.

#### SUMMARY

Selective renal angiography in the dog shows specific changes during acute hemorrhagic hypotension consisting of reduction in caliber of main renal, segmental, and interlobar arteries as well as of the intrarenal veins and the main renal vein. Renal blood flow was diminished as judged by prolonged circulation time and increased reflux of the contrast medium from the renal artery into the aorta. Frequently there was irregularity of the nephrogram, suggesting intrarenal redistribution of blood flow away from the cortex; this phenomenon was seen at levels of mean systemic blood pressure as high as 60 mm. Hg and did not appear to be related directly to the duration of the hypotension. It is suggested that there is a changing pattern of intrarenal blood flow distribution despite the

 $\label{eq:table_IV} T_{\text{ABLE IV}}$  effect of tham in 5 experiments

	Abnormal in			No Change by	Toward	To Control in
	Total	1	1	THAM in	Control in	16 Control in
Main renal artery	3		3		3	
Segmental arteries	5		5	I	1	3
Interlobar arteries	4		4		2	2
Flow	5		5	3	2	
Intrarenal veins	5		5	2	3	
Renal vein	5		5		5	

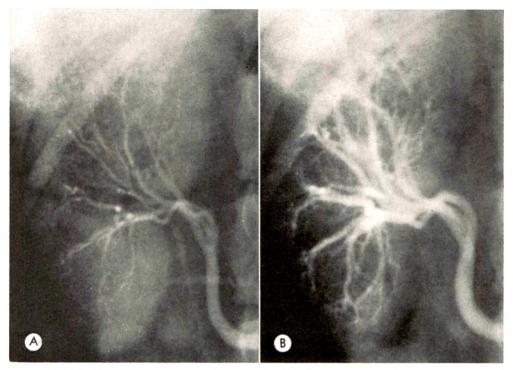


Fig. 6. (A) Control angiogram in a 20 kg. dog; 2 second film. Mean blood pressure is 136 mm. Hg. (B) Animal had been bled 650 ml. with fall in mean blood pressure to 60 mm. Hg, at which time the angiogram showed: diminution in caliber of main renal, segmental and interlobar arteries; slight irregularity of cortical perfusion; and early vein opacification. Now the 2 second film of the angiogram immediately after reinfusion of the blood shows an increase in caliber of the arteries as compared with the control. The kidney also measures slightly larger than in its control state.

maintenance of a constant level of hypovolemic hypotension. Several of the animals showed early opacification of the main renal vein.

Rapid intravenous infusion of isotonic saline in the hypotensive animal usually produced no elevation in the systemic blood pressure and also effected no improvement in the angiographic abnormalities.

THAM administered intravenously to

the hypotensive animal usually effected restitution of some of the angiographic abnormalities toward control appearances; however, the post-THAM angiograms still showed the nephrogram irregularity.

Reinfusion of the blood effected correction of the angiographic abnormalities noted during the hypotension. Actually the immediate post-reinfusion angiograms gave evidence of reactive hyperemia of the kid-

 $T_{\text{ABLE }V}$  changes after blood reinfusion—compared to control—in 10 dogs

	1	1	No Change	Indeterminate
Main renal artery	IO			
Segmental arteries	9		I	
Interlobar arteries	IO			0
Intrarenal veins	I	5	2	2
Main renal vein	3		7	
Flow	6	3	I	

ney as manifested by increased size of arteries and increased blood flow (more rapid vascular phases and less reflux of contrast medium from the renal artery into the aorta). The evidences of intrarenal redistribution of blood flow in hypovolemic shock (nephrogram irregularity) were no longer present after reinfusion of blood.

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# VASCULAR IMPRESSIONS ON THE URETERS\*

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↑ PPARENT extrinsic pressure defects of Arrange of the ureters are frequently encountered on excretory urography and retrograde pvelography. With a few notable exceptions, these usually are dismissed as being of no significance or, more commonly, not even mentioned in the roentgenologic report. If they are noted, they may be attributed to vascular crossing defects but are ordinarily not further defined. Many of these defects reflect important disease; some are of little or no importance or are manifestations of disease processes or anatomic states that are roentgenographically more directly apparent. Indeed some of the groups of ureteral notching discussed below were appreciated only retrospectively.

We propose to review the potential causes of vascular notching of the ureters regardless of their diagnostic importance.

Vascular pressure defects of the ureters may be arterial or venous. A single area of ureteral "notching" may be present or there may be multiple serpentine notching defects along a segment or along all of a ureter. For a diagnosis of vascular impression to be entertained, the defect or defects must be present on all roentgenograms on which the segment of ureter in question is demonstrated and must be more evident on the filled diastolic than on the empty constricted ureter. The defect must furthermore be clearly due to pressure from a structure extrinsic to the ureter. If these criteria are strictly adhered to when considering a diagnosis of arterial or venous

notching of the ureters, the differential diagnosis must be a short one indeed.

Case reports of vascular impressions on the ureters have appeared rather frequently. In virtually each case, multiple differential diagnostic possibilities are presented. These have included: retroperitoneal fibrosis, pressure from retroperitoneal tumor or lymph nodes, ureteritis cystica, tuberculous or chronic nonspecific ureteritis, primary ureteral tumor, ureteral peristalsis, hemangiosarcoma of the ureter, cellular debris, nonopaque calculi, blood clots, and on retrograde studies, air bubbles. 8,9,18,24,25,27,31,33,34,40,44,49-51

Of the above, most are clearly intrinsic in nature. We have found only retroperitoneal tumor or lymph nodes to present a significant differential problem. A single ureteral impression by a crossing vessel or an adjacent vessel can indeed be closely mimicked by retroperitoneal tumor or lymph node. Retroperitoneal fibrosis can, as will be shown below, cause dilatation of collateral veins and resultant vascular indentation upon the ureters, but the typical ureteral compression by the fibrotic process itself bears no relationship to the type of extrinsic pressure caused by crossing vessels. 15,49 Ureteritis cystica, although almost always prominently mentioned in the differential diagnosis of vascular impressions on the ureters, is clearly an intrinsic ureteral disease.

The serpentine type of notching, accounted for by dilatation of the ureteral artery or vein or of the gonadal vein, should in reality never be confused with

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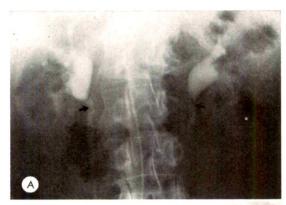




Fig. 1. (A) Intravenous pyelogram with bilateral proximal ureteral notching (arrows). (B) Aortogram demonstrating both ureteral impressions to be due to crossing accessory renal arteries (arrows). It is interesting to note that the impression on the right ureter is in a lateral location. The same vessel accounting for this impression also indents the uretero-pelvic junction as it crosses from medial to lateral.

any of the above intrinsic entities with the possible exception of peristalsis. The fact that peristalsis presents a changing pattern should remove it from consideration in the differential diagnosis.

We have found only 4 intrinsic ureteral entities, all of which are extraordinarily rare, to in any way present a differential diagnostic problem. These are ureteral valves, 46 ureteral diverticulosis, 41 periarteritis nodosa of the ureter, 42 and ureteral sacculation in children with absent abdominal musculature.

The differential diagnosis within the group of vascular impressions is very extensive.

# A. ARTERIAL IMPRESSIONS ON THE URETERS

I. IMPRESSIONS BY ACCESSORY RENAL ARTERIES

Baum and Gillenwater<sup>6</sup> have demonstrated previously poorly understood impressions on the renal pelvis to be due to crossing vessels. In patients with accessory renal arteries, particularly when these arise low from the aorta, similar defects may be found on the proximal ureters. These may be crossing defects or may be extrinsic pressure on the medial or lateral aspect of the ureter (Fig. 1, A and B). Vessels crossing at the uretero-pelvic junction have been implicated in the etiology of uretero-pelvic obstruction.

## 2. COMPRESSION BY THE ILIAC ARTERY

Impressions on the ureters are commonly seen at the level at which they cross the iliac vessels. These extrinsic pressure defects are often deep and seem, at least roentgenographically, to cause minor degrees of obstruction (Fig. 2). Such "obstructions," however, appear not to be clinically significant. When defects of this type appear on the right in the female patient, they may lead to a mistaken diagnosis of "right ovarian vein syndrome" (Fig. 9,  $\mathcal{A}$  and  $\mathcal{B}$ ;  $\mathcal{B}_2$  below).

## 3. RENAL ARTERY STENOSIS

The periodic revival of interest in hypertension of renal vascular origin has sensitized radiologists to the recognition of ureteral scalloping as an indirect sign of renal artery stenosis.2,8,27,34,42,51,55 Such ureteral notching had in fact been thought to be almost pathognomonic of stenosis of the renal artery.8,27 Although this is not so, the sign is nonetheless a valuable one. That vessel which accounts for this type of serpentine notching is the ureteral artery. This complex artery has been largely ignored by the standard anatomy texts, but has been thoroughly described by urologists, gynecologists, and angiographers. It is a long anastomotic channel extending from the kidney to the bladder. It takes multiple origin from: (a) intrarenal dorsal

and ventral branches of the renal artery; and/or (b) an extrarenal branch of the renal artery; (c) the gonadal artery; (d) directly from the aorta; (e) from lumbar arteries; (f) directly from the internal iliac artery; or (g) vesical, uterine, and hemorrhoidal branches of the internal iliac artery<sup>2,10,13,35,45,51</sup> (Fig. 3). Rarely, the renal contribution to the ureteral artery may be seen on a normal renal arteriogram without evidence of notching of the ureter (Fig. 4). It may dilate in chronic pyelonephritis, renal carcinoma, carcinoma of the renal pelvis, and tuberculosis, as well as in renal artery stenosis.<sup>10</sup>

As each of the feeding twigs reaches the ureter, it divides into ascending and de-



Fig. 2. The ureter is frequently indented by the iliac artery as it lies upon this vessel (arrow). Despite the apparent distention of the ureter proximal to the site of crossing, such vascular impressions appear not to be symptomatic.

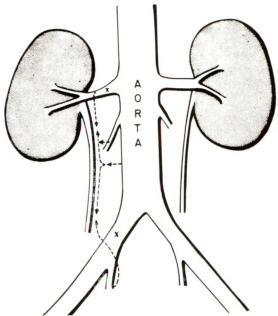


Fig. 3. Sketch of the arterial supply of the ureter. The ureter normally receives its arterial supply from branches of the renal artery, gonadal artery, directly from the aorta, from lumbar arteries, directly from the internal iliac artery, or from branches of the internal iliac artery. As each of these twigs reaches the ureter, it branches into an ascending and descending limb and joins with its neighbors to form a continuous channel. Flow is normally to the ureter from all sources, but direction of flow is responsive to pressure changes. Renal artery stenosis (upper X) may cause dilatation of the ureteral artery and perfusion of the kidney by ureteral arterial twigs feeding into the renal artery distal to the stenosis. Similarly, aortic occlusion or occlusion of the common or internal iliac artery (lower X), with resultant lowered pressure in the pelvis may result in ureteral artery dilatation; flow in this case, however, is from the renal artery to the pelvis.

scending branches and, running in the ureteral adventitia, joins with adjacent branches to form a continous channel. Flow in this channel is normally to the ureter from all sources. Flow is, however, responsive to pressure changes and will take place toward low pressure areas even should this cause the reversal of normal flow direction. Should there be a significant stenosis of the renal artery proximal to the site of origin of a ureteral artery contribution, fall in pressure beyond this stenosis



Fig. 4. Primary roentgen magnification of late arterial phase of normal selective left renal arteriogram. The renal contribution to the ureteral artery is clearly demonstrated (arrows). It is intimately associated with the ureteral adventitia, but causes no impression on the ureter.

may be sufficient to cause a reversal of flow in and dilatation of the ureteral artery, resulting in renal perfusion distal to the site of occlusion. Such dilatation may cause multiple areas of extrinsic pressure on the ureter (Fig. 5, A–D). This is probably the most familiar cause of ureteral notching and when present is thought to suggest a degree of renal artery stenosis sufficient to be implicated in the production of hypertension.

### 4. AORTIC AND ILIAC ARTERY OCCLUSION

The same periureteral arterial channels, which serve to perfuse the kidney beyond a renal artery stenosis or occlusion and which account for the classical picture of ureteral notching, may, under appropriate pressure changes conduct blood in the reverse di-

rection (Fig. 3). Such changes occur in aortic or iliac artery occlusion. The low pressure area is then in the pelvis and flow is from the renal artery through the periureteral arterial channel to the internal iliac artery (Fig. 6, A-C). The resultant notching is rarely as marked as in renal artery stenosis, since many other collateral channels are available for pelvic perfusion and the periureteral vessels do not greatly enlarge. We have not seen ureteral notching previously described as a sign of iliac artery disease, but now that we are alert to this possibility, we have found it to be not infrequently present. It appears unlikely that the amount of blood "stolen" from the kidney is adequate to be implicated in the production of renal vascular hypertension.

# 5. CIRSOID ANEURYSM OF THE RENAL ARTERY

Cases of cirsoid aneurysm of the renal artery causing ureteral impression have been reported.<sup>30</sup> This probably is a real entity; however, one cannot help but wonder whether careful angiographic examination might not demonstrate some of the reported lesions to in fact represent periureteral collateral arteries developing in response to renal artery, iliac artery, or aortic occlusion. Figure 7 is an intravenous pyelogram of a patient reported at surgery to have had such a cirsoid aneurysm. Angiography was not performed.

### 6. IMPRESSION BY AORTIC AND HYPO-GASTRIC ARTERY ANEURYSMS

The rare aneurysm of the hypogastric artery has led to complete occlusion of the ureters and resultant anuria. Before this stage is reached, the enlarging aneurysmal mass will indent the ureter.<sup>7</sup>

Entrapment of the ureters by abdominal aortic aneurysm is common.

# B. VENOUS IMPRESSIONS ON THE URETERS

I. NORMAL GONADAL VEIN CROSSING DEFECT

Both ureters may be crossed by normal gonadal veins (Fig. 10) proximally, a short

distance below the uretero-pelvic junction, and distally, at about the level of S<sub>I</sub>. Crossing defects may frequently be seen at both of these locations (Fig. 8, A and B; and 9, A-C). Should they present a diagnos-

tic problem, selective gonadal venography may be performed. These defects are of no clinical significance except as they may be related to the concept of "ovarian vein syndrome."

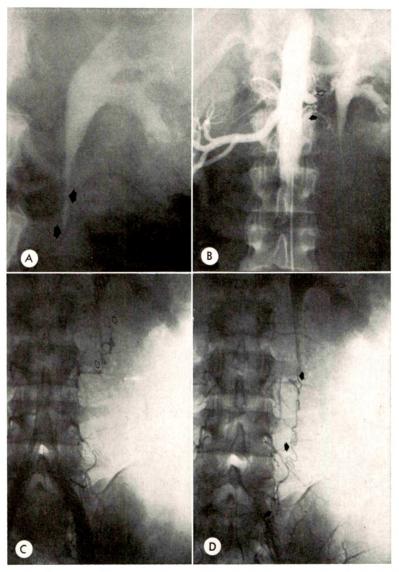
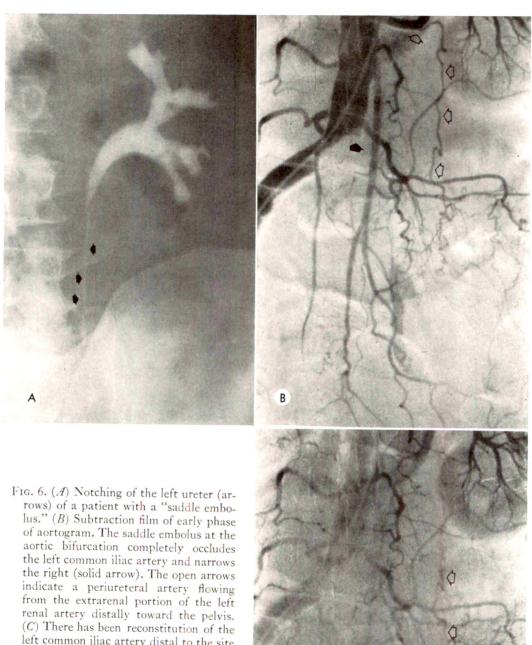


Fig. 5. (A) The proximal ureter of this young hypertensive adult demonstrates rather subtle but quite constant extrinsic impressions (arrows). (B) A midstream aortogram demonstrates almost complete occlusion of the left renal artery (open arrow), probably by fibroplastic disease. The solid arrow demonstrates hypertrophy of the upper lumbar arteries. (C) This reversed tone film of a later stage of the same injection demonstrates the hypertrophied upper lumbar arteries (arrows) to be closely associated with the proximal ureter as they add their contribution to the ureteral artery. (D) A still later stage of the same midstream aortogram, after the aorta and iliac arteries have emptied, demonstrates hypertrophy of the iliac contribution to the periureteral artery (solid arrows). This runs from the pelvis to the kidney and notches the ureter along its course. The open arrow at the top demonstrates intrarenal vascular opacification distal to the site of occlusion shown in B. This filling has been accomplished through the ureteral rather than the major renal artery.



left common iliac artery distal to the site of embolic occlusion (solid arrow). In addition, the periureteral artery has completed its course from the renal artery to the internal iliac artery (open arrows) and participates in reconstitution of the internal iliac artery. The ureteral notching in such cases is more prominent in long standing occlusions, but the flow phenomenon is demonstrated very early.



Fig. 7. Excretory urogram of a patient said at surgery to have had a cirsoid aneurysm of the right renal artery. Persistent extrinsic pressure on the

#### 2. RIGHT OVARIAN VEIN SYNDROME

Dilatation of the right ureter with associated urinary tract infection in a previously gravid woman is often ascribed to pressure upon this structure by an aberrant dilated right ovarian vein, incompletely involuted. The level of ureteral impression is said to be at S1. 12,31,42 Although there have been documented cases of improvement of symptoms following ligation of the right ovarian vein in such patients (Fig. 9. A-C), the validity of this mechanism remains open to question.21 It is difficult to accept ureteral stasis as being due to dilated ovarian veins, since in no other instance of venous notching have we seen ureteral compression account for significant ureterectasis or infection. Bartley and Chidekel4 have demonstrated clear imprints as wide as 12 mm. on the left ureter, due to gonadal vein crossing in women with pelvic

proximal ureter was present on all roentgenograms (arrows). Whether this is a real entity or a manifestation of unrecognized compensatory periureteral vascular hypertrophy remains open to some question.

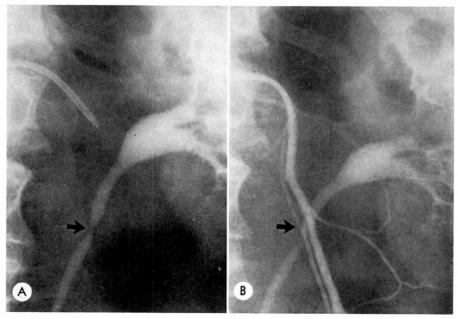


Fig. 8. (A) Excretory urogram with crossing defect of the left ureter (arrow). (B) Selective left spermatic venogram demonstrating the defect to be due to the crossing of the ureter by the smaller of a pair of spermatic veins (arrow).

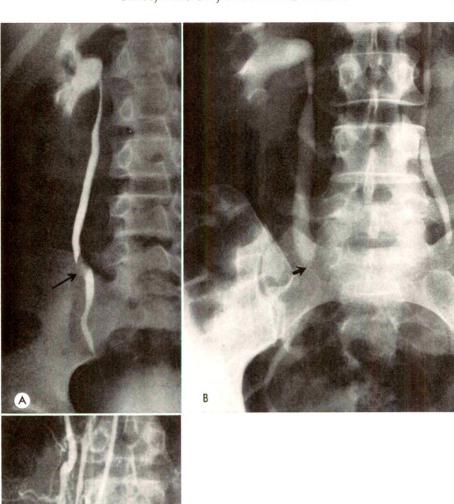




Fig. 9. Right ovarian vein syndrome. (A) It is difficult to differentiate between the oblique impression on the ureter of the crossing of a normal common iliac artery and (B) the more vertical crossing of a gonadal artery. The patient represented in B did indeed have mild ureterectasis, persistent infection and flank pain and was said to have right ovarian vein syndrome. She was helped by venous ligation. (C) Selective right ovarian venogram in a patient with a coincidental uterine leiomyoma. This normal ovarian vein crosses the ureter at the level of SI in a vertical position. Every vascular impression on the right ureter at the level of SI does not, therefore, represent a right ovarian vein syndrome.

varicosities. None had hydroureter or hydronephrosis or were infected.<sup>4</sup> Indeed, many of the published excretory urograms in patients reported to have this entity demonstrate the course of the indentation to be more consistent with the oblique iliac artery crossing (Fig. 2; and 9, A–C) than with the vertical gonadal vein crossing.

# 3. VARICOCELE AND VARICES OF THE BROAD LIGAMENT

There are multiple theories to account for the occurrence of varicocele in the male and varicosities of the broad ligament in the female as being almost invariably a left-sided process. 19,20,24,39 The vertical and longer course of the left gonadal vein as compared with the right is frequently implicated, as is the entrance of the left gonadal vein into the left renal vein at a right angle as compared with the entrance of the right gonadal vein into the inferior vena cava at an oblique angle. Pressure on the iliac portion of the left gonadal vein by the descending colon has been blamed for causing stasis in this system. Some investigators have claimed to have found valvular absence or valvular insufficiency in the left gonadal vein.

The most ingenious, and perhaps most satisfying explanation to account for this lateralization also depends upon the different anatomic relationships of each gonadal vein to the inferior vena cava, the corresponding renal vein, and to neighboring arterial structures (Fig. 10; and 11, A-D). The right gonadal vein usually empties into the inferior vena cava below the renal vein, although it may occasionally enter the latter.8 The left gonadal vein almost invariably enters the left renal vein. The left renal vein passes anterior to the aorta and posterior to the superior mesenteric artery in a position above the transverse duodenum. The aorta and superior mesenteric artery form the 2 arms of a potential "nutcracker" which may narrow the left renal vein as it passes between them (Fig. 11, A-D), much as the transverse duodenum is narrowed in duodenal ob-

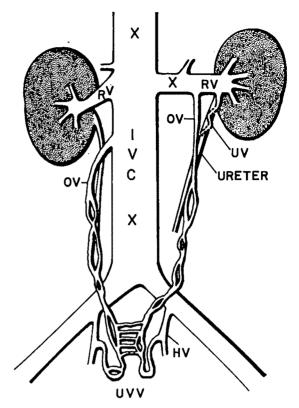
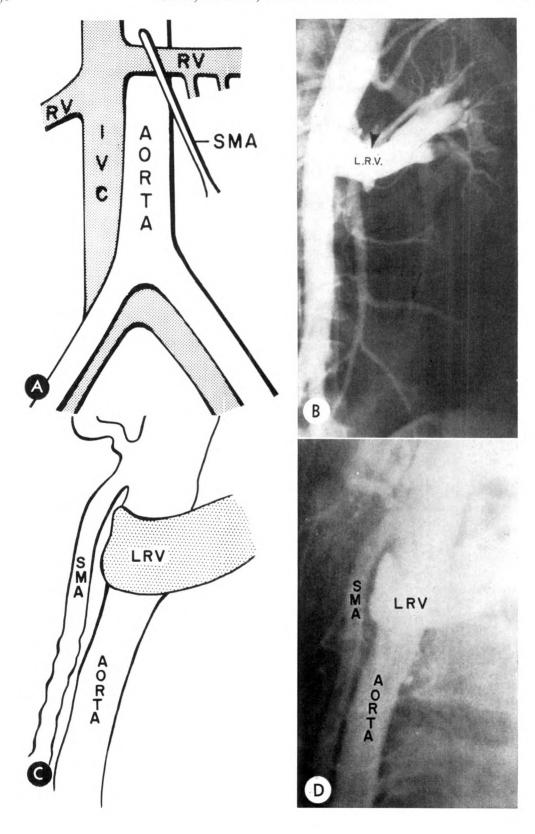


Fig. 10. Sketch of abdominal, renal, and periureteric venous anatomy. The left gonadal vein (ovarian vein in the sketch) almost invariably empties into the left renal vein, while the right empties into the inferior vena cava below the right renal vein. The ureteral veins generally empty into the renal veins at a location peripheral to the site of gonadal emptying. Either of these 2 latter structures is capable of causing ureteral notching either of a serpentine nature or of a simple extrinsic pressure type. Free communication between them has been noted on multiple occasions. The ovarian veins are in free communication in the broad ligament with the uterine veins and therefore with the hypogastric and iliac veins. It will be seen therefore that occlusion or stenosis of the inferior vena cava above the renal veins, below the renal veins, or in the renal veins (sites marked X) is capable of altering flow in the gonadal or ureteric veins and thereby accounting for vascular notching. RV =renal vein; OV=ovarian (gonadal) vein; UV =ureteral vein; HV=hypogastric vein; UVV =uterine veins; X=sites of occlusion.

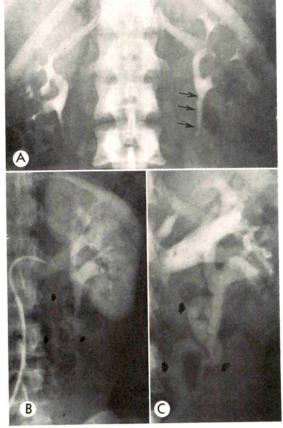
struction in the so-called "superior mesenteric artery syndrome." 19,20,39,52 Obstruction to flow at this point in the left renal vein may be transmitted as increased pressure to the gonadal and ureteric veins. Free



communication between these 2 sets of veins has been demonstrated and both have been found to be dilated in patients with varicocele.<sup>31</sup>

In the patient represented in Figures 11, A-D, and 12, A-C we demonstrated a 3 cm. water gradient across the renal vein measured at the level at which it was crossed by the superior mesenteric artery. Renal venous washout time was 12 seconds as compared with the normal upper limits of 3 seconds. In this patient, there was retrograde filling and dilatation of a periureteral vein demonstrated both in the venous phase of the aortogram and selective left renal arteriogram as well as in the selective left renal venogram.

There is considerable support for this "nutcracker" theory in the work of Vassilev<sup>52</sup> who demonstrated stagnation of con-



wrapped around the left ureter, clearly accounting for the notching. We therefore abandoned the diagnosis of hypertension on a renal vascular basis (although there has been at least one report of hypertension experimentally produced by means of renal venous stenosis<sup>14</sup>). We do believe that this notching phenomenon is probably related to varices of the broad ligament, or, in the male, to varicocele.

Fig. 12. (A-C) This young hypertensive woman presented with distinct ureteral notching not only in the proximal ureter as demonstrated in (A) (arrows) but throughout the entire ureter. It was thought that her hypertension might well be explained on the basis of renal artery stenosis with resultant ureteral artery hypertrophy. However, the arterial phase of the midstream aortogram and of the selective left renal arteriogram was entirely normal. On the venous phase of (B), selective arteriography, and on (C), selective left renal venography, a tortuous, periureteral vein (arrows) was seen descending along and

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Fig. 11. (A) Sketch of relationship of left renal vein to aorta and superior mesenteric artery (SMA), frontal projection. As the left renal vein runs toward the inferior vena cava, it lies anterior to the aorta and posterior to the superior mesenteric artery, in the jaws of a potential "nutcracker." (B) Simultaneous aortogram and selective left renal venogram demonstrating the angiographic representation of this anatomic condition (LRV=left renal vein). "Standing fluid waves" are incidentally noted in the superior mesenteric artery. (C) Lateral sketch of the superior mesenteric artery-aortic "nutcracker." The left renal vein (LRV) is frequently seen at autopsy to be flattened at the site at which it is crossed by the superior mesenteric artery. (D) Simultaneous aortogram and selective left renal venogram as seen in the lateral projection demonstrating the angiographic equivalent of sketch C. The mechanism of duodenal compression in "superior mesenteric artery syndrome" depends upon similar anatomic relationships.

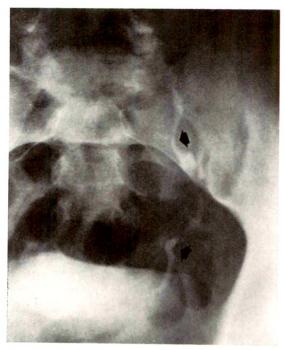


Fig. 13. Extrinsic ureteral indentations (arrows) in patient with varicocele.

trast material at the point of crossing of the superior mesenteric artery on direct injection of varicoceles. At autopsy, the left renal vein is frequently noted to be flattened precisely at this point.<sup>19</sup>

The relationship of varicocele in the male to subfertility has kindled new interest in this area.<sup>39</sup> Figure 13 represents the opacified notched distal left ureter of a patient with varicocele. Intravenous pyelograms are not usually obtained in otherwise normal varicocele patients, but the finding of notched ureters in some that have been so studied has been striking.<sup>24,55</sup> It has been suggested that an imprint on the left ureter of more than 5 to 6 mm. width should lead to suspicion of the presence of pelvic varicosities or varicocele.<sup>4</sup>

Sporadic reports of varicosities of the ureter with scalloping appear from time to time without an etiology having been established. 9,25,31,40,44,47,48,50 While some of these may in fact be "idiopathic," it may be that some were related to otherwise undetected varicocele or varices of the broad ligament. Hematuria, generally painless, has been present in many of these patients.

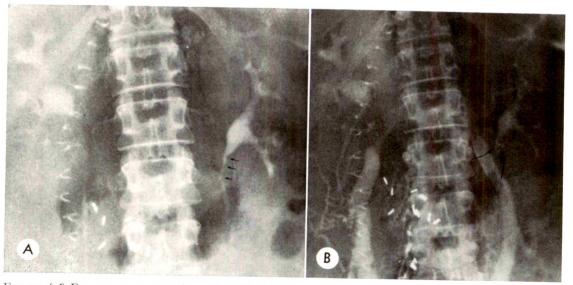


Fig. 14. (A) Excretory urogram of a patient who had undergone a mesocaval shunt for the management of portal hypertension. The inferior vena cava has therefore been divided. The left ureter is notched (arrows). (B) Bilateral femoral venous injection demonstrating in addition to massively widened gonadal veins, multiple plexiform retroperitoneal veins, at least one of which, and probably others, notches the left ureter (arrows).

4. OCCLUSION OF THE INFERIOR VENA CAVA
BELOW THE RENAL VEINS

The inferior vena cava may be occluded below the renal veins for a variety of reasons including tumor, clot, retroperitoneal fibrosis, and surgery in patients having plication or ligation for pulmonary embolization, 22,49 or as part of a mesocaval shunt as management of portal hypertension. In all of these instances, flow from the lower extremities must take place through collateral veins. 5,26 Some of these collaterals will be the lumbar and ascending lumbar veins running in the retroperitoneum, communicating superiorly with the azygos system.21,43,53 The latter drains into the superior vena cava, bypassing the occlusion and returning blood to the right heart via the superior vena cava. During their course in the retroperitoneum, these enlarged collateral veins may run adjacent to and cross the ureters and indent them<sup>23</sup> (Fig. 14, A and B).

Occlusion of the cava or iliac veins need not be complete in order to create dilatation of retroperitoneal collaterals, as illustrated in Figure 15, A and B. This patient had retroperitoneal metastases from an ovarian tumor. The resultant ureteral impression is not due to direct pressure from the metastatic mass but rather to collateral channels enlarged because of tumor compression of the left iliac vein. Similarly, the ureteric notching described in retroperitoneal fibrosis is usually not due to the primary disease but to iliac and caval com-

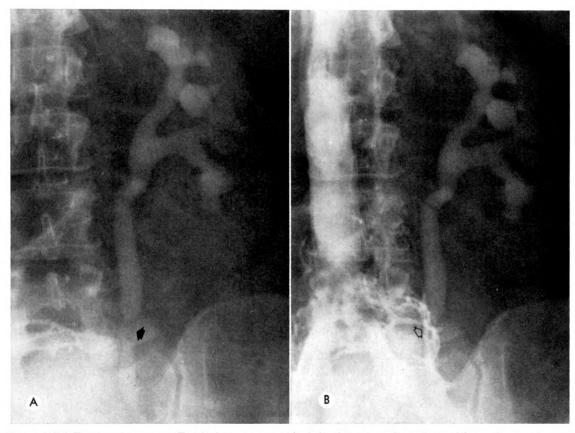


Fig. 15 (A) Excretory urogram. Extrinsic pressure on the left mid ureter of a patient with ovarian carcinoma metastatic to the retroperitoneum (arrow). (B) Inferior vena cavagram. The extrinsic pressure defect is seen to be due to collateral venous channels bypassing an area of incomplete occlusion, rather than to the metastatic tumor itself (arrow).



Fig. 16. Inferior vena cavagram of a patient with pancreatic carcinoma metastatic to the liver. A metastatic deposit almost entirely occludes the inferior vena cava. There is resultant regurgitant flow into both renal veins and down a widened left gonadal vein (vertical arrow). This is in position to cause extrinsic pressure upon the left ureter, although an actual crossing defect attributable to the gonadal vein is not demonstrated in the illustration. It is likely that the notching of the ureter that is demonstrated in this illustration (horizontal arrow) is due to retroperitoneal-azygos collaterals (see also Fig. 14, 20, and 21).

promise by the fibrotic process causing dilatation of collateral vessels.<sup>49</sup>

Other common collateral pathways in occlusion of the inferior vena cava below the renal veins are the periureteral and gonadal veins draining blood from the pelvis into the inferior vena cava or renal veins above the site of occlusion (Fig. 10). These vessels are intimately related to the ureters and are even more likely to cause ureteral notching than are the ascending lumbar and azygos collaterals.

# 5. OCCLUSION OF THE INFERIOR VENA CAVA ABOVE THE RENAL VEINS

Occlusion of the inferior vena cava above the renal veins may be due to thrombus or tumor, particularly tumor metastatic to the liver. If such a metastatic deposit is strategically located adjacent to the inferior vena cava as it courses through the diaphragm, antegrade caval flow will be compromised and ureteral impressions may be caused by ascending lumbar and other retroperitoneal collaterals enlarging as they divert flow into the azygos system. In addition, prevention of normal emptying of the renal veins may cause reversal of flow in and dilatation of the gonadal and periureteric veins<sup>21</sup> with resultant vascular notching (Fig. 16).

## 6. RENAL VEIN OCCLUSION

A renal vein may be compromised or occluded by thrombosis, by extension of hypernephroma, by malignant disease metastatic to the lymph nodes adjacent to the renal vein, and by direct extension of retroperitoneal tumor. The involved kidney does not usually infarct but remains viable by virtue of collateral venous drainage. 11,30,36 Several potential routes of drainage have been described. When one of the drainage channels is the ureteral vein, a serpentine type of ureteral notching may result<sup>18,54</sup> (Fig. 10; 17, A and B; and 18, A and B) —the radiographic equivalent of the varicocele felt by the clinician. The arteriovenous shunting found in some hypernephromas tends to accentuate collateral flow and encourage reversal of flow in the ureteric and gonadal veins with resultant dilatation.

## 7. OCCLUSION OF THE AZYGOS VEIN

Tumor in the posterior mediastinum may occlude the azygos and hemiazygos veins causing retrograde flow from the azygos system through the ascending lumbar veins to the inferior vena cava (Fig. 19).

In addition, the ascending lumbar vein on the left is frequently in direct communication with the left renal vein as a remnant of the embryologic left "renal collar," a communication between the subcardinal and supracardinal systems. 21,29,32,38 When this communication is present (68.8 per cent, Anson *et al.*3) increased flow in the ascending lumbar system may be directly

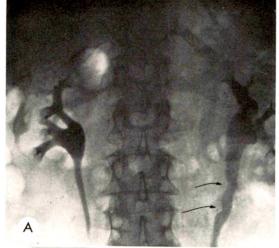




Fig. 17. (A) Intravenous pyelogram of a patient with a left hypernephroma, demonstrating deep serpentine left ureteral notching (arrows). The left renal vein was occluded by tumor. The extensive arteriovenous shunting in this lesion occasioned more marked dilatation of the periureteral veins than is usually seen with renal vein occlusion from other causes. (Reprinted from Renal Angiography, edited by O. W. Kincaid. Year Book Medical Publishers, Inc. Used by permission.)
(B) Intravenous pyelogram of a patient with renal vein thrombosis. Notching is not as marked as in A, but the mechanism is identical. (Reprinted with permission of Radiology.<sup>11</sup>)

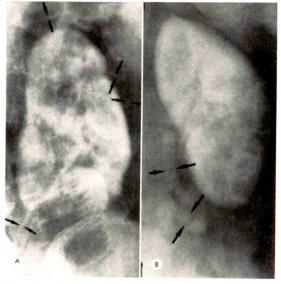


Fig. 18. (A) Renal vein thrombosis. Venous phase of selective renal arteriogram. There are multiple collateral channels available (arrows) for drainage of the kidney when the renal vein is thrombosed. When one of the channels is the periureteral vein, notching may occur (lowermost set of arrows). (B) Venous phase of selective renal arteriogram. Renal vein occlusion by tumor, as in the case of this patient with pancreatic carcinoma metastatic to the left renal pedicle, will have results similar to those of occlusion by nonmalignant thrombus. The arrows indicate the large draining gonadal or periureteral vein which accounted for notching of the ureter. (A and B reprinted with permission of Radiology.<sup>11</sup>)

transmitted to the left renal vein and thence to the periureteric and gonadal veins. This lumbar renal communication is not present on the right.<sup>3</sup>

The reversal of flow in the azygos system has been considered to be a sign of inoperability of mediastinal tumor. This may be best demonstrated on intraosseous azygography (Fig. 20).

## 8. OCCLUSION OF THE SUPERIOR VENA CAVA

Occlusion of the superior vena cava, usually occurring as a result of tumor, causes enlargement of collateral veins bypassing the area of occlusion to allow drainage of blood from the head and upper extremities to the right atrium. Some of these collateral channels drain in a retrograde fashion into the azygos group of veins, through the posterior mediastinum and

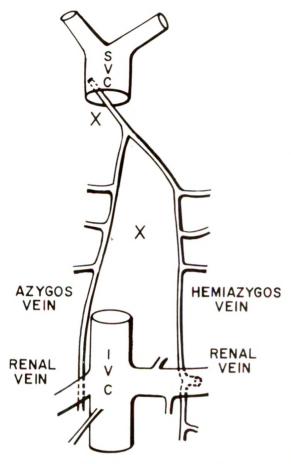


Fig. 19. Sketch of the azygos system and its relationships to the superior and inferior venae cavae. Occlusion of the azygos system in the posterior mediastinum (lower X), or occlusion of the superior vena cava between the site of emptying of the azygos into the superior vena cava and the right atrium (upper X) may account for reversal of flow in the azygos system with retrograde filling of the ascending lumbars and retroperitoneal vessels. These hypertrophied vessels filling in a retrograde fashion can account for notching of the ureter. There is an additional mechanism available for collateral flow on the left, since the left azygos system or ascending lumbar system frequently communicates directly with the left renal vein. Increased pressure in this retroperitoneal system may be transmitted to the renal vein and thereby to the gonadal or periureteral vein, accounting for notching on a slightly different basis. This mechanism is not available on the right.

retroperitoneum into the ascending lumbar veins and inferior vena cava to reach the right atrium<sup>26,28,53</sup> (Fig. 19). As they lie in the retroperitoneum, ureteral notching may occur (Fig. 21, A–C).

(As early as 1947, there was speculation as to the existence of this mechanism without actual roentgenographic demonstration.<sup>47</sup>)

### 9. PORTAL HYPERTENSION

In many patients with portal hypertension, spontaneous splenorenal, gastrorenal, and mesenteric renal anastomoses occur and some degree of portal decompression

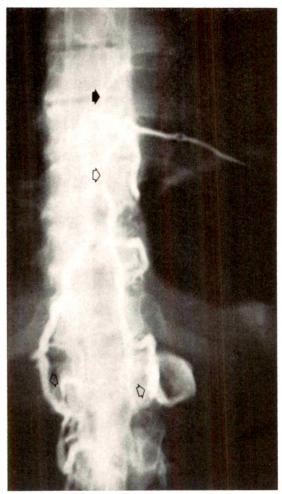


Fig. 20. Intraosseous azygogram in a patient with bronchogenic carcinoma metastatic to the posterior mediastinum. Antegrade flow of contrast material into the azygos vein has been prevented by the occluding retroperitoneal tumor. There is very minimal antegrade flow (solid arrow). Most of the flow occurs distally through the azygos and hemiazygos systems into the ascending lumbars (open arrows). In addition, on the left, there is some filling of the renal vein. This is not unexpected since a remnant of the left "renal collar" does persist in a large percentage of persons.

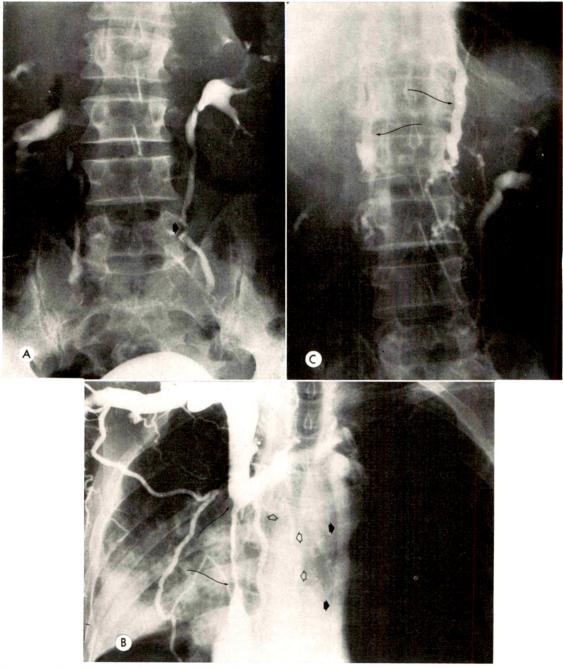


Fig. 21. (A) Intravenous pyelogram of a patient with a superior vena cava syndrome. An unusual indentation on the left ureter is seen at the arrow. (B) On superior vena cavagraphy, there is almost complete tumor occlusion of the superior vena cava below the entrance of the azygos vein (long arrows). In addition to the presence of multiple superficial collateral veins, there is retrograde flow through the azygos (open arrows) and a massively dilated accessory hemiazygos vein (solid arrows). (C) Late roentgenogram of the abdomen during the same injection demonstrates the azygos flow (long arrows) to drain in a retrograde fashion into multiple retroperitoneal collaterals, at least one of which (open arrow) is intimately connected with the left ureter at the site of impression seen in A (solid arrow).

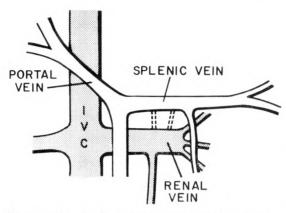


Fig. 22. Sketch of relationships of the portal system to the left renal vein. Multiple potential collaterals exist between the systemic venous system and the portal venous system: among others, splenorenal anastomoses (dotted lines). In portal hypertension, or in carcinoma of the pancreas, these potential collaterals may function as a route for portal decompression. The elevated portal pressure may be transmitted to the renal vein with resultant reversal of flow in the gonadal or periureteric system, thereby accounting for ureteral notching.

takes place through the left renal vein<sup>21</sup> (Fig. 22). These large channels probably represent distention of pre-existing communications between the renal veins and the portal system.<sup>3,16,17</sup> In the frog, and in the mesonephric stage of the human embryo, as well as in the early metanephric stage of certain mammals, there is a renal portal stage.32,33 These anastomoses will themselves frequently exert sufficient pressure on the renal pelvis and ureter to be recognizable as filling defects on excretory urography (Fig. 23). More dramatically, in a small number of patients, elevated portal pressure transmitted to the left renal vein, is sufficient to reverse flow in the gonadal and periureteric veins resulting in their dilatation and accounting for the serpentine type of ureteral notching identical with that seen in renal vein thrombosis.42 Hematuria has been reported in such cases.33

Less frequently, plexiform retroperitoneal spleno-azygos collaterals unrelated to the renal, gonadal, or ureteric veins may enlarge as portal collaterals. These may cause impressions on the ureter, usually *not* of a serpentine nature.

## IO. CARCINOMA OF THE PANCREAS

Pancreatic carcinoma frequently occludes veins coursing through it. This sign of venous occlusion must in fact be present for the angiographic diagnosis of carcinoma of the pancreas to be made with confidence. The splenic vein is often occluded by carcinoma of the body and tail of the pancreas because of its close anatomic relationship to this organ. The same collateral channels which function as a route for spontaneous portal decompression in patients with portal hypertension on a cirrhotic basis are available in some cases of malignant occlusion of the splenic vein depending upon the site of occlusion.16 Figure 24, A and B illustrates collateral drainage partially through retroperitoneal veins wound about the upper of a left pair of ureters.

#### SUMMARY AND CONCLUSIONS

Impressions upon the ureters accounted for by extrinsic pressure defects exerted by

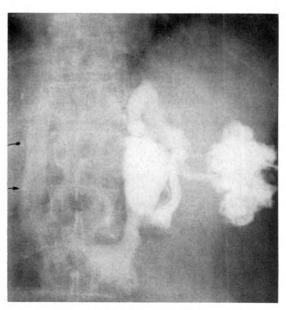


Fig. 23. This patient with portal hypertension underwent percutaneous splenoportography which demonstrated the presence of spontaneous splenorenal shunting and filling of the inferior vena cava (arrows). This is a common phenomenon and although this case did not show actual ureteral notching, notching on this basis, with hematuria, has been reported.

adjacent or crossing arteries and veins are frequently noted on urographic studies. The observation of these extrinsic pressure defects is usually made, but their significance is often overlooked. We have discussed and illustrated those conditions which may result in ureteral notching on an arterial and venous basis.

The arterial causes of ureteral impressions include:

- impressions by accessory but normal renal arteries;
- compression by a normal iliac artery;
- 3. renal artery stenosis;
- 4. aortic and iliac artery occlusion;
- 5. cirsoid aneurysm of the renal artery;
- 6. impression by a ortic and hypogastric artery aneurysm.

The venous impressions on the ureters may be due to:

- normal gonadal vein crossing defect on right or on left;
- 2. right ovarian vein syndrome;
- 3. varicocele and varices of the broad ligament;

- 4. occlusion of the inferior vena cava below the level of the renal veins by tumor, clot, retroperitoneal fibrosis, or following caval division as part of a surgical procedure;
- 5. occlusion of the inferior vena cava above the level of the renal veins due to thrombosis or tumor;
- 6. renal vein occlusion by thrombosis, hypernephroma, malignant disease metastatic to the area of the renal vein or by direct extension of retroperitoneal tumor;
- occlusion of the azygos vein by tumor:
- 8. occlusion of the superior vena cava by tumor;
- 9. portal hypertension;
- -10. carcinoma of the pancreas.

We do not feel that the long differential diagnosis usually appended to case reports of ureteral notching is a realistic one. The only real differential diagnostic problem is that of retroperitoneal tumor or lymph nodes. With this one exception, vascular impressions on the ureters should be recognized as such. However, the choice among

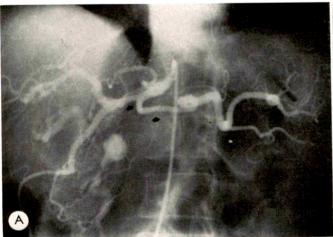
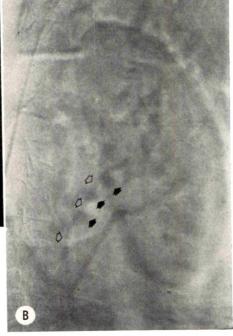


FIG. 24. Arterial phase of selective celiac arteriogram of a patient with carcinoma of the body of the pancreas. Tumor encasement is seen in the common hepatic and splenic arteries (arrows). (B) Subtraction film of venous phase of selective celiac arteriogram. There is a duplication of the collecting system on the left. The upper of these 2 ureters is indicated by the open arrows. The solid arrows



indicate a tortuous vessel coursing along this left ureter and causing extrinsic pressure notching.

the large number of possible vascular defects may be difficult or impossible on the basis of urography alone. The proper angiographic study, chosen on the basis of all available clinical and roentgenographic information, will usually supply the diagnosis.

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# THE BIOCHEMICAL BASIS OF THE SKELETAL CHANGES IN CHRONIC UREMIA\*

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WHILEstudying agroup of patients with chronic uremia undergoing peritoneal dialysis, I reviewed the literature dealing with the skeletal changes in chronic azotemia. In general, I found a good deal of confusion in the radiologic literature and a tendency to describe roentgen findings, e.g., sclerosis, as isolated entities with little reference to the underlying biochemical abnormalities. 6,7,9,11,12,24,34,48,49,52,53

The purpose of this paper is to present a logical analysis of the various skeletal changes in chronic uremia in the light of the dynamic biochemical alterations. To accomplish this end, a brief review of bone mineralization and the various hormones involved in skeletal turnover is appropriate.

## GENERAL CONSIDERATIONS

Bone formation is a dual process consisting of the formation of a protein matrix (osteoid) and the deposition therein of bone mineral. Normally, both activities go on simultaneously. The matrix is made up of two principal elements: (a) a collagenous fibrillar protein; and (b) an amorphous mucopolysaccharide ground substance which loosely concentrates calcium on its surface. The role of the osteoblast seems to be the laying down of a calcifiable collagen fibril in an appropriate ground substance. The factors controlling osteoblastic activity are poorly understood at present.

Bone mineral consists of hydroxyapatite crystals [3Ca<sub>3</sub>(PO<sub>4</sub>)<sub>2</sub>·Ca(OH)<sub>2</sub>] onto the surface of which are adsorbed the various ions in the extracellular fluid space. The parallel arrangement of the crystals along the long axis of the collagen fibrils facilitates exchange of ions between bone and body fluids. Because the crystals are mi-

nute (25 Å-1,500 Å), they have a large surface area relative to their mass: *i.e.*, the total surface area of the bone crystals comprising the skeleton of a 70 kg. man is estimated to exceed 100 acres.

The body fluids are supersaturated with respect to Ca++ and PO4- ions, so that normally new bone collagen is readily calcified independent of the parathyroid glands. Indeed, the net removal of Ca++ and PO4 ions from the extracellular fluid is largely determined by the available calcifiable matrix. If this is true, why doesn't calcification go on indefinitely? A number of hypotheses have been offered to explain this seeming paradox. According to Deakins,31 there is a natural barrier to unlimited apatite deposition because most of the bone crystals lie within hollow collagen fibrils. The quantity of mineral taken up is limited by the volume of the collagen fibrils. As calcification proceeds, the water content of the mineral phase progressively decreases to a point where the crystals no longer exchange ions by diffusion. At this point, mineralization ceases.

Plasma calcium is composed of 3 fractions:

- 1. A non-diffusible, inactive moiety bound to protein as calcium proteinate
- 2. The active, diffusible ionic calcium
- 3. A small, diffusible, nonionic fraction complexed with citrate (<1 mg. per cent). This complex prevents precipitation of calcium phosphate from solution by reducing the Ca<sup>++</sup> ion concentration. By binding calcium in this way, citrate also facilitates solution of bone mineral at comparatively high pH levels.

At normal plasma protein levels, approximately half of the calcium is present

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in ionic form and the other half in a loose, undissociated complex with protein.<sup>28</sup> This relationship may be expressed by the mass law equation.

$$K = \frac{(Ca^{++}) \times (protein^{**})}{(Ca \ proteinate)} \ .$$

Accordingly, the ratio of ionized to unionized calcium remains constant, regardless of alterations in total plasma calcium, if the concentration of protein does not change.

In 1923, Robison discovered an enzyme, alkaline phosphatase, which splits off inorganic phosphate from organic phosphorus compounds. We now differentiate a number of phosphatases on the basis of their activity at various pH ranges.

A. Osteoblasts elaborate an alkaline phosphatase with maximal activity at pH 9.4 which diffuses into the blood stream and is excreted by the liver. Although small amounts of the enzyme are found in cartilage, kidney, brain, spleen and intestine, bone is the principal source of this alkaline phosphatase in the plasma. This has been demonstrated experimentally by the lack of appreciable change in the plasma enzyme level after evisceration of the intestines, liver and spleen.

B. 5<sup>1</sup>-nucleotidase, an alkaline phosphatase with maximal activity at pH 7.5. This enzyme specifically catalyzes the removal of phosphate from certain nucleotides, e.g., adenosine monophosphate.35 Elevated serum levels of 51-nucleotidase are found in patients with liver disease who have an elevated total alkaline phosphatase. Although the latter may also be increased in diffuse skeletal disease, the nucleotidase level is usually normal in the latter situation. The determination of 51-nucleotidase may, therefore, be helpful in patients with skeletal disease in whom there is a question of associated hepatic involvement, e.g., metastatic carcinoma. In the absence of liver disease, the 51-nucleotidase level should be normal.

C. There are several acid phosphatases, so-called because the pH of their optimal activity is on the acid side of neutrality.

One of these enzymes is found in mammalian erythrocytes, another in the prostate and at least two others in bone. The cell of origin of the acid phosphatases in bone is thought to be the osteoclast. An increase in plasma acid phosphatase may occur in diffuse skeletal disease where the total alkaline phosphatase level is high, e.g., Paget's disease, hyperparathyroidism.

# THE ACTIONS AND ROLE OF PARATHORMONE

The primary function of parathormone is to maintain the ionic concentration of calcium in the plasma and extracellular fluid within rather narrow limits, in spite of wide fluctuations in calcium intake and excretion.<sup>31</sup> In turn, the secretion of parathormone is controlled by the plasma ionic calcium level.

There are 4 peripheral sites of action of parathormone—the kidney, skeleton, gut and mammary gland. For purposes of simplicity, I shall omit consideration of the mammary gland.

- 1. Kidney. Parathormone acts directly upon renal tubular epithelium to produce a prompt phosphaturia by inhibiting phosphate reabsorption. This results in a fall in plasma phosphate which, in turn, raises the level of plasma calcium. The rising plasma calcium "turns off" further parathormone secretion. In addition parathormone enhances tubular reabsorption of calcium.
- 2. Bone. Parathormone also acts directly upon bone to stimulate resorption, a complex process in which matrix and collagen fibers are resorbed along with bone mineral. In addition to calcium, this also releases the products of collagen dissolution which are excreted in the urine as hydroxyproline-containing peptide fragments. Hence, determination of urinary hydroxyproline, an amino acid unique to collagen, may occasionally be helpful in the diagnosis of hyperparathyroidism.<sup>21</sup>
- 3. Gut. The effect of parathormone on the

gut will be considered in connection with vitamin D.

# ACTIONS AND ROLE OF VITAMIN D AND THE RELATIONSHIP BETWEEN VITAMIN D AND PARATHORMONE

It has long been known that vitamin D, probably in the form of an active metabolite, promotes the absorption of calcium from the gut. There is also experimental evidence to suggest that vitamin D stimulates the synthesis of RNA and protein in the gut mucosa to produce a specific calcium binding protein.<sup>50</sup> The latter plays an undetermined role in the absorption of calcium from the intestinal mucosa. Parathormone also promotes the absorption of calcium from the gut but there are important biologic differences in the actions of these 2 substances.<sup>20,31,32,47</sup>

- 1. Parathormone produces a greater fall in the plasma phosphate level.
- 2. Vitamin D produces a greater excretion of calcium in the urine.
- 3. The time responses of these actions are quite different. While parathormone effects a prompt excretion of phosphate and potassium, the phosphaturia produced by vitamin D comes on slowly and is not accompanied by excretion of potassium.

Recent mitochondrial studies suggest that vitamin D and parathormone act synergistically to promote the release of calcium. In this relationship, vitamin D has an independent direct action upon bone and must be present before parathormone can exert its effect on bone. On the other hand, parathormone acts directly upon the renal tubule, independent of vitamin D, to promote the excretion of phosphate. What is the functional significance of this relationship? The synergistic interaction of parathormone and vitamin D assures an adequate concentration of calcium in the plasma and extracellular fluid, as well as a sufficient supply of Ca++ and PO<sub>4</sub>= ions in the extracellular fluid for normal calcification of newly formed bone collagen.32 In

this interplay, parathormone is responsible for maintaining a normal calcium concentration, while vitamin D is concerned with providing sufficient calcium and phosphate ions for calcification of newly deposited bone collagen.

Logically, therefore, parathyroid hyperplasia should be an important physiologic response to vitamin D deficiency. The degree of hyperparathyroidism depends upon the severity of the vitamin D deficiency. In mild vitamin D deficiency, the increased circulating parathormone can maintain a normal plasma calcium level at the expense of a low plasma phosphate, presumably due to decreased sensitivity of bone to parathormone. The latter necessitates an increased amount of circulating parathormone which in turn leads to a phosphate diuresis and a low plasma phosphate level. In marked vitamin D deficiency, however, the parathyroids cannot significantly enhance either absorption of calcium and phosphate from the gut or their resorption from bone. On the other hand, the increased parathormone continues to act directly upon the renal tubules to influence tubular handling of calcium, potassium, magnesium and phosphate and their distribution between the intra and extracellular fluid spaces.

# ACTIONS AND ROLE OF THYROCALCITONIN

In 1962, Copp and his co-workers<sup>8</sup> reported the existence of calcitonin, a new calcium regulating hormone. Although originally thought to be secreted by the parathyroid glands, it has been clearly shown that the hormone has its origin in the ultimobranchial body and the thyroid gland. Embryologically, the latter organs have a common anlage in the fifth pharyngeal pouch. In various fishes, amphibians and birds, the ultimobranchial body persists as a separate structure; in mammals, however, it becomes incorporated into the thyroid gland where the parafollicular or C cells secrete the hormone in response to hypercalcemia

Calcitonin acts both on the skeleton and

the kidney. It acts on the skeleton by inhibiting bone resorption. When bone resorption is inhibited, calcium continues to enter the skeleton from the plasma, resulting in hypocalcemia. Calcitonin also increases urinary excretion of phosphate. What is the role of calcitonin in man? The answer is not entirely clear at present. However, the available evidence suggests that calcitonin plays a role in bone remodeling and in modulating the plasma and extracellular concentration of calcium in conjunction with parathormone. 8,16,29,37

# THE BIOCHEMICAL ABNORMALITIES IN CHRONIC UREMIA

There is incontrovertible evidence of defective bone mineralization in chronic uremia. 14,15,17 This leads to rickets or osteomalacia depending on the age of the patient. The rickets and osteomalacia secondary to chronic renal disease are indistinguishable roentgenologically and histologically from their counterparts due to primary vitamin D deficiency. 7,39,42,43

What is the pathogenesis of the abnormal mineralization? A number of hypotheses have been advanced to explain the defective mineralization.

- It has been suggested that a low Ca×PO<sub>4</sub> product (<40) is responsible for the defective mineralization. In this regard, Stanbury and Lumb<sup>43</sup> have reported a series of 79 uremic patients with defective mineralization in whom the plasma Ca×PO<sub>4</sub> product varied from 16–85. There are numerous other case reports in the literature with low, normal or high plasma Ca×PO<sub>4</sub> products. Obviously, the defective mineralization cannot be due to an abnormal plasma Ca×PO<sub>4</sub> product per se.
- 2. Excessive loss of calcium in the urine or feces secondary to metabolic acidosis.

  Albright and Reifenstein¹ claimed that uremic acidosis fostered hypercalcuria. More recently, Stanbury and Lumb⁴² have shown that urinary calcium falls to low levels (<100 mg. daily) when

the glomerular filtration rate is markedly reduced. Furthermore, urinary calcium excretion is not materially influenced by correction of the acidosis.

Also, according to the studies of Stanbury and Lumb<sup>42</sup> fecal excretion of calcium is not excessive in these patients; fecal calcium tends to parallel dietary calcium and uncommonly exceeds the latter by more than 50 mg. Moreover, Nordin's<sup>30</sup> work suggests that chronic small losses of calcium produce osteoporosis rather than osteomalacia or rickets.

3. Direct effect of uremic acidosis upon bone.

There is no evidence that uremic acidosis interferes with bone mineralization or accelerates dissolution of the mineral already deposited on the collagin fibrils. Likewise, correction of the acidosis does not cure the rickets or osteomalacia, although it may reduce the negative calcium balance (principally by decreasing the amount of calcium lost in the feces).<sup>25,42</sup>

4. Abnormal metabolism of vitamin D.

Stanbury has demonstrated a profound deficiency of calcium absorption from the gut in patients with chronic uremia, unrelated to urinary calcium excretion, the presence or absence of metabolic acidosis, the plasma level of calcium and phosphorus and the degree of parathyroid activity.39,41,43 The deficient intestinal absorption of calcium associated with rickets or osteomalacia and the correction of these abnormalities by large doses of vitamin D suggest an acquired insensitivity to the biologic effects of the vitamin. 13,26,39 At present, we do not definitely know whether this is due to an abnormal metabolism of vitamin D, the presence of a vitamin D antagonist or an effect of the uremic state on biochemical mechanisms involving vitamin D at the cellular level.44 However, there is suggestive evidence that uremic patients form biologically inert polar metabolites<sup>2</sup> of vitamin D.

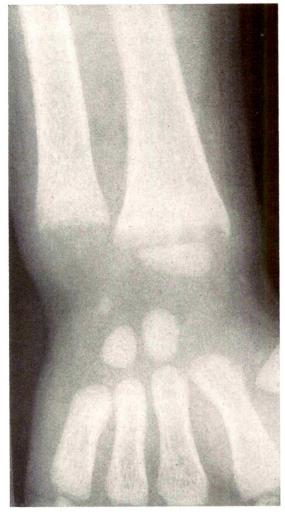


FIG. 1. Wrist of  $2\frac{1}{2}$  year old boy with renal tubular acidosis showing florid rickets. Plasma calcium 8.2 mg./100 ml.; plasma phosphorus 2.0 mg./100 ml.; alkaline phosphatase 30 Bodansky units.

# ROENTGEN MANIFESTATIONS OF SKELETAL DISEASE IN CHRONIC UREMIA

Let us now examine the roentgen findings in the skeleton, knowing that patients with chronic uremia have an acquired insensitivity to vitamin D along with parathyroid hyperplasia—the latter a compensatory response to vitamin D deficiency. Let us further assume that we are dealing with a spectrum of disease and not with sharp end points; *i.e.*, varying severity of renal disease, varying levels of acquired insensi-

tivity to vitamin D, varying degrees of parathyroid hyperplasia and fluctuations in the natural history of these biologic parameters.

#### RICKETS AND OSTEOMALACIA

Since the basic abnormality in chronic azotemia is an acquired insensitivity to vitamin D, the resulting skeletal disease is characterized by deficient mineralization of osteoid; i.e., rickets or osteomalacia, depending upon the age of the patient. In young patients prior to epiphyseal closure, there is typical disorganization of proliferating epiphyseal cartilage due to failure of provisional calcification.14 The fundamental histologic and roentgenologic findings are indistinguishable from those of nutritional rickets<sup>17,38,39</sup> (Fig. 1; and 2). In older patients, osteomalacia occurs with characteristic osteoid seams in the trabeculae of the diaphyseal spongiosa.4,15,17 In its florid form, osteomalacia may be reflected by decreased skeletal density, Looser zones, and secondary bone deformities<sup>46</sup> (Fig. 3). It is important to remember that roentgen examination of the skeleton is a gross technique. Hence, it is possible that some patients with mild osteomalacia may exhibit no recognizable skeletal changes by roentgenography; i.e., patients with bone pain, tetany, muscle weakness etc.

#### SECONDARY HYPERPARATHYROIDISM

Since parathyroid hyperplasia is an important physiologic response to vitamin D deficiency, increased osteoclasis and osteitis fibrosa usually accompany azotemic rickets and osteomalacia. At times, the secondary hyperparathyroidism may be mild and, hence, undetectable roentgenologically. The predominant roentgen findings in such patients are those of rickets or osteomalacia. More commonly, in long-standing renal failure, osteitis fibrosa is the predominant process histologically and roentgenologically. Radioimmunoassays by Berson and Yalow<sup>5</sup> indicate that the level of circulating parathormone in these pa-

tients with secondary parathyroid hyperplasia is frequently greater than in many patients with primary hyperparathyroidism. Oddly enough, plasma calcium levels may vary considerably and are frequently in the hypocalcemic range. Classically, we have been taught that the hypocalcemia of chronic renal failure is due to the high plasma phosphate level secondary to reduced glomerular function. Undoubtedly, this is true of the hypocalcemia of acute renal failure. However, the hypocalcemia in chronic azotemia may be associated with low normal levels of plasma phosphate.<sup>3</sup> Does thyrocalcitonin play a role here?

The skeletal changes in secondary hyper-



FIG. 2. Knee of 6 year old male with Fanconi syndrome and characteristic changes of rickets in the zones of provisional calcification.



Fig. 3. Right femur of a 55 year old female with renal tubular acidosis. Note the over-all decreased density, indistinct trabecular margins and Looser zone indicative of osteomalacia.

parathyroidism are indistinguishable from those of primary hyperparathyroidism. The roentgenographic findings, therefore, may include subperiosteal resorption of bone (best seen in digital phalanges, outer third of clavicle, medial aspect of proximal tibia, sacroiliac joints, symphysis pubis), a motheaten, granular appearance of the skull, resorption of the lamina dura, "bone cysts"  $^{45}$  (Fig. 4, A–C).

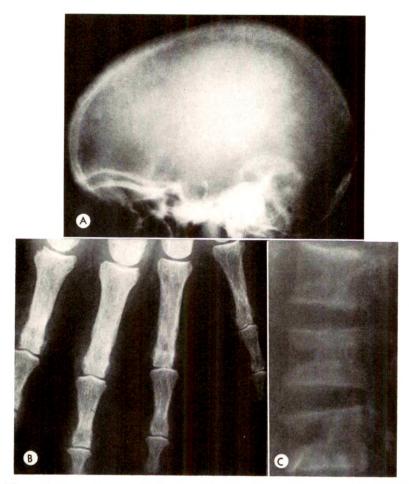


Fig. 4. (A-C) The patient, a 57 year old female with chronic uremia, demonstrates skeletal changes of osteomalacia and secondary hyperparathyroidism with the latter predominating. Note the characteristic "moth-eaten" appearance of the skull in A, the phalangeal subperiosteal bone resorption in B, and the "rugger-jersey" spine in C.

It follows from the above discussion that some patients may exhibit the roentgen findings of rickets or osteomalacia, others the findings of hyperparathyroidism and still others, a mixture of the findings of both diseases.

## WHAT ABOUT OSTEOSCLEROSIS?

Although azotemic bone sclerosis was originally reported by Hamperl and Wallis in Germany in 1933, 19 it was not described in the U.S. until 1941. Since that time, in spite of increasing interest in this subject, it appears to be the single most mystifying roentgen finding in chronic uremia. As such, there have been a number of un-

supported explanations offered for its existence. Indeed, one gets the impression from the radiologic literature that osteosclerosis is a unique, unexplained finding that should be accepted empirically. Let us examine the various theories that have been put forth:

1. There is no evidence to support the claim that osteosclerosis is secondary to long-standing anemia. This hypothesis was advanced by Crawford *et al.*<sup>10</sup> because of the anemia in chronic renal failure along with sclerosis in prominent sites of bone marrow activity; *i.e.*, lumbar spine, pelvis and skull. Histologic examination of these areas, however, dem-

- onstrates diminished rather than increased erythropoietic activity.
- 2. There is likewise no evidence to incriminate metabolic acidosis *per se* as the cause of the osteosclerosis.
- 3. Although rarely, the removal of a parathyroid adenoma may trigger a reparative response characterized by an overswing of the pendulum<sup>36</sup> (i.e., localized osteosclerosis at the site of previous bone destruction), hyperparathyroidism in an osteoblastic phase does not explain the finding of generalized osteosclerotic mineralized bone. In this regard, Wills et al.51 reported a patient with chronic renal insufficiency who exhibited the roentgen findings of osteosclerosis and hyperparathyroidism. It is interesting that removal of a large parathyroid adenoma in this patient resulted in regression of the bony absorption but the osteosclerosis remained unchanged.
- 4. There is evidence, however, in support of a marked over-all increase in osteoid formation and a relative resistance of osteoid tissue to the erosive influence of parathormone.
- a. Garner and Ball,<sup>17</sup> in a study of iliac cancellous bone in 16 patients with azotemic osteomalacia, found the mean volume of whole bone matrix (mineralized plus unmineralized) to be twice that of normal controls. Indeed, these investigators estimate that some of their patients produced as much as 3 kg. of osteoid. In some patients, the mineralized bone by histologic determination was increased. Ball and Garner<sup>4</sup> suggest that this may be due to an increased amount of woven bone which mineralizes when lamellar bone does not. Perhaps this also explains the increased calcium content of the lumbar vertebrae in uremic osteosclerosis reported by Kaye et al.22,23 Two other explanations have been offered to explain the findings of Kaye et al.23 which suggest that uremic osteosclerosis is due to an increased mass of mineralized bone: fluctuations in the degree of osteomalacia and

- vitamin D resistance may permit periodic more efficient utilization of dietary calcium and phosphorus; and complete demineralization of bone before sectioning may abolish differences between osteoid and fully mineralized bone. (Kaye *et al.*<sup>23</sup> do not specify whether they sectioned the tissue while it was undecalcified.)
- b. Matrait and his co-workers<sup>27</sup> also reported both an increased volume of osteoid and an increased total volume of bone matrix in biopsy specimens of iliac crest in some patients with nutritional osteomalacia. Since the histologic and roentgenologic findings in children with azotemic and nutritional rickets are indistinguishable, is there a common denominator (i.e., the net increase in bone mass due to rapid body growth) to explain the defective mineralization in the face of a positive mineral balance? Does the hyperostosis, present in some adults with chronic renal failure, bear the same relationship to the development of osteomalacia that accelerated body growth bears to the production of rickets in children? Is the low ash of malacic bone the result of excessive osteoid rather than a negative calcium and phosphorus balance?
- c. A correlation of the roentgen and histologic findings in uremic osteosclerosis demonstrates markedly thickened trabeculae indicative of an over-all increase in bone mass (Fig. 5, A and B).
- d. Harrison et al.<sup>20</sup> have clearly shown that ordinary doses of parathormone have no influence upon the plasma levels of calcium and phosphate in the vitamin D deficient rat. This can readily be changed by correcting the vitamin D deficiency. Also Rasmussen et al.<sup>32</sup> have demonstrated that parathyroidectomy in vitamin D deficient rats produces a sharp rise in plasma phosphate with no change in the plasma calcium level. These changes can be prevented by the prior administration of 2–3×the amount of parathormone necessary to maintain a

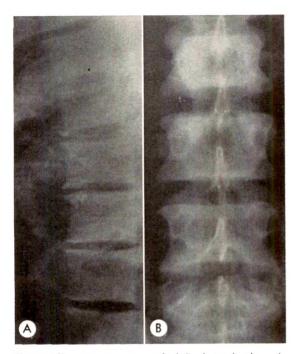


Fig. 5. Roentgenograms of (A) lateral thoracic spine and (B) anteroposterior lumbar spine showing osteosclerosis. Note the over-all increased bone density and the poorly defined, thickened trabeculae. The patient was a 26 year old man with chronic azotemia due to long-standing pyelonephritis.

normal plasma phosphate level in the D-fed animal. It appears, therefore, that the D-deficient rat is excreting phosphate maximally because of increased endogenous parathormone production. It is clear that parathyroid hyperplasia is present both in D-deficient rats and humans with vitamin D deficiency. It is also clear that there is sufficient endogenous hormone in both instances to maintain a high degree of control over phosphate metabolism. Yet the hormone has little calcium mobilizing activity under these circumstances. Furthermore, the failure of either exogenous parathormone administration or parathyroidectomy in the D-deficient rat to elevate the plasma calcium level is not due to depletion of bone calcium since D-deficient and D-fed rats have a comparable bone ash. These data strongly support the concept of an acquired resistance to vitamin D in chronic uremia.

WHAT IS THE EXPLANATION FOR THE "RUGGER-JERSEY" VERTEBRA?

The word "rugger" is a synonym for rugby; the phrase "rugger-jersey" refers to the alternating striped shirt commonly worn by British rugby teams. The term "rugger-jersey sign" has been used to describe the increased density of the upper and lower margins of the vertebral body separated by a central horizontal zone of decreased density (Fig. 6). A review of the cases of "rugger-jersey" spine in chronic uremia described in the literature and a study of the several cases I have personally



Fig. 6. Lower thoracic spine in a 45 year old man showing the characteristic appearance of the "rugger-jersey" spine; *i.e.*, banded sclerosis adjacent to the vertebral plates alternating with decreased density of the mid vertebral bodies.

seen indicate that these patients have both chronic osteomalacia and hyperparathyroidism. I would, therefore, propose the following hypothesis. It is well known that vertical growth of a vertebral body occurs by enchondral bone formation in the superior and inferior cartilaginous plates. The latter may be compared with the epiphyseal end plates of a tubular bone. Perhaps like the latter, they have an increased blood supply (Reynolds<sup>33</sup> has suggested a similar explanation for the characteristic end plate deformities in sickle cell anemia). The blood supply of the end plates favors the deposition of increased osteoid in these areas in patients with acquired vitamin D resistance. The mineralized bone (central vertebral radiolucent band) subjacent to the osteoid is more susceptible than the latter to the erosive effect of the increased circulating parathormone.

#### SUMMARY

- 1. A brief review of bone mineralization and of the hormones involved in skeletal turnover is presented.
- 2. Also presented is a discussion of the biochemical abnormalities associated with chronic renal failure.
- 3. An attempt is made to correlate the biochemical abnormalities with the skeletal changes demonstrable by roentgenography. Basically, patients with chronic uremia develop a resistance to vitamin D which results in rickets or osteomalacia. The latter in turn is responsible for compensatory secondary hyperparathyroidism.
- 4. Fluctuations in the rickets osteomalacia and the secondary hyperparathyroidism, and predominance of one process over the other adequately explain the roentgen findings.
- 5. A hypothesis is offered to account for the "rugger-jersey" appearance of the spine.

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the roentgenographic material in a series of patients with chronic uremia undergoing dialysis.

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## ANGIOGRAPHY IN THE EVALUATION OF PATIENTS FOR ABDOMINAL AORTIC SURGERY\*

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THERE are three common miscon-L ceptions about arteriography in surgical diseases of the aorta: (1) that it is very difficult and dangerous; (2) that it is inaccurate when compared to operative findings; and (3) that it is unnecessary because the diagnoses are usually clinically

It is our purpose to show that the principal value of aortography is not to make basic diagnoses but to provide a detailed evaluation which aids in difficult decisions of management. Furthermore, we submit that accuracy can be achieved when suitable care is taken in obtaining and interpreting the study. Finally, we find that these procedures are not unusually difficult or hazardous.

Since 1963, we have used aortography in over 1,200 patients as part of the evaluation of aorto-ilio-femoral disease. We have reviewed the angiograms in 288 who had severe aortic abnormalities. In this report we stress the effect of arteriographic findings on therapeutic decisions. As useful as angiography has been in the past, we believe that its value will increase as we adopt a greater variety of surgical procedures, learn more about the natural history of aortic diseases, and become more sophisticated in our interpretation of arteriograms.

#### MATERIAL AND METHOD

Serial abdominal aortography has been part of our routine evaluation of all pa-

tients with suspected arterial disease below the aortic arch since 1963. Alternate biplane filming has been available since 1965. The abdominal aortogram is usually only one step in the examination, which may also include a thoracic aortogram, pelvic and peripheral lower extremity arteriograms, selective visceral injections, and studies of the veins. Arterial pressure measurements, and, more recently, ultrasonic A and B-scans are sometimes obtained at the same time.

Percutaneous retrograde femoral artery catheterization with a J-tip catheter is employed if a satisfactory pulse is present at the groin. Otherwise, translumbar aortography with a teflon catheter-needle is the first alternative when a high abdominal aortogram will suffice. It may be combined with a non-catheter retrograde femoral injection for distal aortic visualization.15 Percutaneous axillary artery catheterization (from the left with a straight, and from the right with a tortuous aorta) is utilized if the other methods are not practical, or if selective arteriography is required.

Films are exposed initially at a speed of 2-3/second, and later at a rate of 1/second, so that a total of 8 exposures spans a period of 4-6 seconds. A bolus of 30-50 ml. 60 per cent methylglucamine iothalamate (conray) or diatrizoate (renografin 60) is injected in 1-1.5 seconds with an automatic injector.

Of 2,300 abdominal aortograms, over

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1,200 have been for the evaluation of primary arterial disease. From these we have selected 288 patients whose code cards indicated the presence of serious abnormality of the abdominal aorta, and reviewed their angiograms and case summaries (Table 1). With repeat examinations there were 316 aortograms. Patients with small or medium sized plaques or sacculations, and minor degrees of diffuse dilatation of the aorta were excluded, as were those with significant disease limited to the visceral or iliac arteries.

# RESULTS AORTIC OCCLUSIVE DISEASE

Angiography was highly reliable in establishing the level and length of occlusions. Although the majority of lesions began just below the renal artery, translumbar aortography proved uniformly successful, since a high puncture (at T12-L1) is used routinely in our department. Detailed visualization of the iliac vessels in several instances required the use of reactive hyperemia (with blood pressure cuffs on both thighs) to increase circulation to the lower extremities.<sup>21</sup>

Stenoses were demonstrated by retrograde femoral catheterization in 21 cases. As in the experience of Friedman *et al.*, <sup>16</sup> a

Table I

AORTIC LESIONS DIAGNOSED BY ANGIOGRAPHY

Occlusive disease		69
Complete occlusion	13	
Severe stenosis	27	
Thrombosis	4	
Occlusive disease, postoperative	25	
Aneurysm		151
Large arteriosclerotic (7 cm.+)		
Small arteriosclerotic (4-7 cm.)	43	
Other types	5	
Diffuse ectasia	22	
Other disease		68
Severe arteriosclerosis		
Dissection	12	
Arteritis	6	
Total 288		

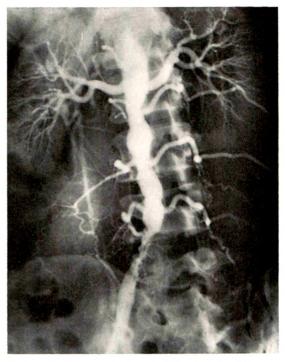


Fig. 1. A 28 year old man with mild claudication. Aortogram shows scalloping of the aortic wall typical of aortitis, a stenosis of the right common iliac artery, and occlusion of the left common iliac artery.

good femoral pulse was frequently present even in patients with severe symptoms, and the catheter could be advanced through tight stenoses. One problem was that the disease shown by angiography was often not quite as dramatic as that found subsequently at surgery. The demonstration of a pressure gradient, particularly during reactive hyperemia, was a useful finding in cases in which the aortogram showed a lesion of doubtful significance (Fig. 1).

In recent years we devoted particular attention to evaluation of the thickness of the aortic wall, in an effort to exclude patients with pipe-like vessels who are not suitable candidates for direct aortic surgery. The finding of a heavily calcified wall along with a thin lumen provided a significant clue.

Acute aortic thrombosis was superimposed on severe atheromatous disease. Retrograde femoral catheterization was possible, since the pulse was not completely

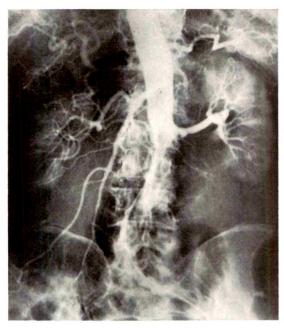


Fig. 2. A 70 year old woman with sudden onset of cold lower extremities.

Arteriogram shows fresh thrombus obliterating the aortic lumen below the renal arteries. The thrombus was easily traversed by the catheter.

obliterated, and the catheter readily traversed the fresh clot (Fig. 2). However, as in the experience of Bell<sup>3</sup> treatment was unsuccessful, with the exception of one patient with partial thrombosis of the aortic wall that responded to prolonged anticoagulation therapy.

Postoperatively, retrograde catheterization was only used when end-to-end grafts had been inserted, and these were negotiated without difficulty. With the more usual onlay grafts (side-to-end, end-to-side) the femoral approach was avoided even when bounding femoral pulses were present. The translumbar aortogram not only confirmed the clinical evidence of patency of the graft, but also showed tendency to kinking, early development of pseudo-aneurysms, and the progression of arteriosclerosis in the patient's vessels proximal and distal to the graft.

#### ANEURYSMS

Biplane aortography and pelvic arteriography were performed on all patients ad-

mitted for elective and semi-emergency resections of abdominal aneurysms. While angiography was used on occasion to rule out aneurysm in a patient with various combinations of an uncoiled aorta, paraaortic mass, flaccid abdomen and/or lordotic spine, physical examination by a skilled clinician, combined with plain film roentgenograms and ultrasound Ascanning<sup>17</sup> markedly reduced the incidence of negative studies in recent years.

Angiography proved very useful in determining the extent of an aneurysm, its proximity to the renal arteries, its involvement of iliac arteries, and, on occasion, provided early clues of a leak (Fig. 3A). Aberrant renal arteries arising below the aneurysm were identified, and associated occlusions or aneurysms of visceral or peripheral arteries were often found. Evaluation of the aortic arch permitted recognition of reparable lesions of the neck arteries, which were usually corrected before elective aneurysm repair.

In patients with small, asymptomatic aneurysms (4–6 cm.), the shape, *i.e.*, a long fusiform dilatation *versus* a sharp saccular bulge, was sometimes a consideration whether to recommend surgery. In poor risk patients with moderate size (6–8 cm.) aneurysms, the likelihood of easy resectability (such as a good margin below the renal arteries) and the absence of significant additional disease (*e.g.*, brachiocephalic or visceral artery stenoses) were considered favorable factors for operation.

Patients with suspected leaking aortic aneurysms had emergency aortographies, provided they were not in shock. It was found that the clinical diagnosis of leaking aneurysm can easily be made erroneously. Older patients frequently have small aneurysms along with unrelated causes for retroperitoneal pain or bleeding. Pancreatitis, ruptured renal cyst and metastatic tumor were among the conditions found in acutely ill patients with pulsatile aortas. On the other hand, when a leaking aneurysm was confirmed, the patient was immediately transferred to the operating

room, and the angiogram was used to advantage during surgery to define anatomy obscured by hemorrhage.

A primary mycotic aneurysm due to Salmonella was diagnosed and localized accurately, permitting successful surgery. This case has been reported elsewhere.<sup>28</sup> Pseudoaneurysms following aortic resection, and an aneurysm in a homograft were also encountered.

Diffuse aortic ectasia to a diameter of 4–6 cm. was seen most often as an incidental finding in patients with peripheral vascular occlusive disease. These individuals frequently had similar dilatation of the iliac, femoral and popliteal arteries, and aneurysms of these vessels were not uncommon. However, the occlusive pattern appeared typically arteriosclerotic, not embolic, as has been suggested.<sup>31</sup> Recognition of diffuse ectasia rather than fusiform aneurysm avoided surgery in a few cases.

#### OTHER DISEASES

Severe arteriosclerosis without significant aneurysm or stenosis was encountered frequently in patients with peripheral occlusive disease. A few of these persons had a clinical course or roentgenologic picture that remotely suggested atheromatous emboli. However, most of the cases had typical arteriosclerotic plaques in the lower extremity vessels. Moreover, 2 patients with documented atheromatous emboli had only mild irregularity of the aortic wall on aortography.

Patients with aortic dissections routinely had both thoracic and abdominal aortography. In 12 of 14 cases the dissection extended into the abdomen, and compression of the true lumen was demonstrated. In 7 patients one of the major visceral arteries was supplied by the dissection. A femoral entry site was used routinely, and the false lumen was entered and injected at some time during the procedure in 4 cases, without complication. In only 1 case was axillary puncture necessary in order to enter the true lumen. The relation of the dissection to the renal arteries and other visceral



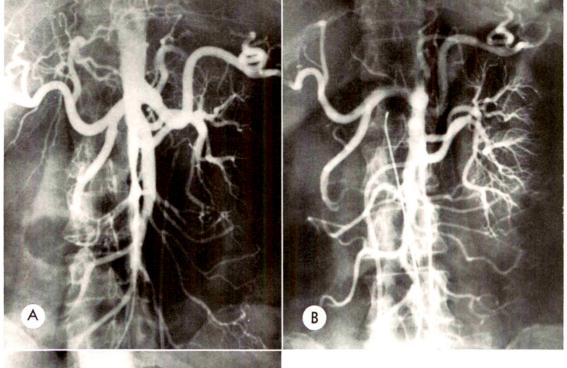


Fig. 3. A 77 year old man admitted for elective evaluation of aortic aneurysm.

(A) A large saccular lesion is seen, with a soft tissue density extending to the left (arrows). On this basis, a leak was suspected. (B) An ultrasonic B scan (transverse section at L<sub>4</sub>) confirms the presence of an aneurysm, with a left posterolateral leak.

branches was the most important information gleaned from these studies (Fig. 4, A-C).

Although aortitis has been most often described in Africa, 18,20,35 and in the



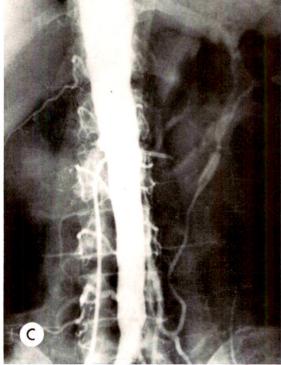


Fig. 4. A 61 year old female with previous right nephrectomy, recent aortic dissection, and 12 hours of anuria.

(A) The true lumen is compressed but patent, as are the 2 left renal arteries. A catheter in the patient's bladder suddenly began draining urine as the procedure was being completed. (B) A repeat study was performed 8 days later, when the patient once more became anuric. This time the lumen could not be entered from the right femoral artery. A catheter passed from the left side shows further occlusion of the true channel, which is now isolated from the thoracic aorta. (C) With injection in the false lumen, the right renal artery, several lumbar arteries, and the inferior mesenteric arteries are seen.

Orient,<sup>29</sup> all of our patients were American born Caucasians of both sexes, ranging from 15–41 years in age. The mildest case in which we had histologic proof was in a

15 year old boy, who had merely irregularity of the distal aorta (Fig. 5). The other cases were associated with significant renal, iliac or other major vessel occlusion. A

16 year old girl with severe renal and mesenteric artery involvement as well as aortic narrowing was found at surgery to have a marked perivascular inflammatory reaction suggesting retroperitoneal fibrosis.

#### COMPLICATIONS

Minor complications such as transient decrease of pulses, local hematomas or roentgenologically evident but clinically inapparent dissections occurred in 14 of the 316 aortographies. There was one serious complication. An obese, hypertensive 75 year old woman with a symptomatic aneurysm had aortography via the femoral route. Following removal of the catheter. local hemostasis could not be obtained. The patient had to be taken to the operating room where a suture was placed in the femoral artery. Because of this incident and her precarious condition, it was decided to postpone the aortic surgery for a week; 36 hours before the rescheduled operation she suddenly ruptured the aneurysm and died.

#### DISCUSSION

In discussing the advances in arterial surgery in the last decade, DeBakey<sup>10</sup> lists angiography first. Nonetheless, there are still a few surgeons who are thoroughly confident of their ability to evaluate arterial disease by clinical examination and surgical exploration. Their mistakes are sometimes shown only by postoperative angiography.

In order to justify its use, arteriography must be both safe and effective. With the use of proper precautions such as a soft, J-tip catheter, and low concentration contrast media, the risk appears not much greater than in angiography in general. Effectiveness is best assured when the procedure is performed by an experienced examiner in a well equipped angiographic room, and the examination is individualized to clarify the patient's particular problem. We disagree with the safety-oriented radiologist who attempts to substitute the hazy shadows of an intravenous aortogram for a real map of the arteries, and the time-

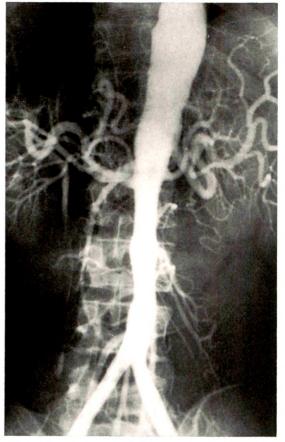
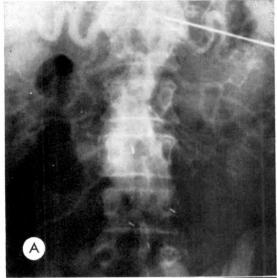


Fig. 5. Aortitis in a 15 year old boy. Minimal scalloping is seen.

conscious surgeon who settles for a quick roentgenogram under anesthesia just before surgery in place of a complete examination. Poor arteriography can be misleading, and therefore worse than no arteriography at all.

Our recent experience with aortic aneurysms confirms our previous impression of the value of aortography.<sup>22</sup> The simple retrograde femoral approach appears to have increasing acceptance.<sup>5</sup> It has long been known that aneurysms 7 cm. or larger are much more likely to rupture than those 6 cm. or smaller.<sup>9</sup> Nonetheless, numerous studies have shown that fewer than I patient in 7 rupture their aneurysms.<sup>6,23,30,33,34</sup> In one of the most analytical recent reviews, Bernstein *et al.*<sup>4</sup> note the problem of increasing frequency of diagnosis, and the late complications which must be added



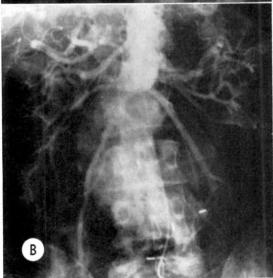


Fig. 6. A 63 year old man with a small asymptomatic aortic aneurysm first detected in 1957, and followed with plain roentgenography and angiography.

(A) Translumbar aortogram in 1962 shows a small fusiform aneurysm. (B) Aortogram in 1966 reveals increase to 11.5 cm. Resection was performed at this time.

to the significant immediate surgical mortality. They conclude that "the increment in survival rates between treated and untreated patients is much less than we had hoped it would be. The incidence of rupture in the small asymptomatic aneurysm is considerably less than the risk of an elective operation."

The life expectancy of patients with aortic aneurysms is usually brief, but it is other problems which lead to death. The individual patient with an asymptomatic aneurysm still presents a painful decision to the clinician, and an accurate aortographic picture of both the lesion and the other arteries can be helpful in reaching the proper conclusion. The small aneurysm may well be followed with plain film roentgenograms or ultra-sound, and perhaps occasional angiography, until rapid enlargement or clinical symptoms present definite indications for surgery (Fig. 6,  $\mathcal{A}$  and  $\mathcal{B}$ ).

The need for operation in leaking aneurysms is more clear cut, for once an aneurysm starts to rupture, it rarely ceases.9 When a patient is bleeding massively, his only chance for survival is immediate surgery, and there is no time for arteriography. However, the majority of leaking aneurysms do not present in this catastrophic manner, and most reports stressing the need for a dramatically speedy trip to the operating room19,25,27 fail to make the distinction. Furthermore, there is little comment on the number of cases that were rushed to surgery that did not have a leak, although one report19 notes that 3 of their cases did not even have an aneurysm. Our experience indicates that angiography need not delay surgery more than 1-2 hours, and that, in addition to displaying some very important anatomy, the arteriogram has a potentially significant role in diagnosing the non-leaking aneurysm or nonleaking non-aneurysm.

In some other areas, the results of aortography have been less rewarding. The ability of the surgeon to reconstruct aorto-iliac occlusions largely depends on the condition of the vessel wall. With the availability of alternative procedures such as axillo-femoral<sup>26</sup> or crossover femoro-femoral<sup>14</sup> bypass grafts, we had hoped to develop criteria which might spare some patients abdominal exploration, but have not been entirely successful so far.

Similarly, we anticipated that the aorta

covered with friable cholesterol deposits causing atheromatous emboli could be radiologically identified. Since further angiography or surgery are contraindicated once the diagnosis is made,<sup>7,8</sup> an early clue on the aortogram would be most helpful. Unfortunately, these deposits do not deform the aortic wall nearly as much as the old, sclerotic plaques and scars that have very little tendency to embolize.

With increasing experience, the diagnosis of aortitis has become considerably easier. We do not know whether this disease is an autoimmune disorder as has been proposed,<sup>29</sup> but agree that it has a worldwide distribution.<sup>12</sup> Our cases had predominantly aorto-iliac involvement, with segments of narrowing and dilatation frequently producing a characteristic scalloped appearance. We believe that some of the cases reported as "congenital abdominal coarctation"<sup>2,11</sup> may well be sequelae of aortitis.

Like aortic aneurysms, the therapy of aortic dissections has been the subject of agonizing reappraisals.1,24 Surgery under optimal conditions in selected patients carries a 1 year mortality close to 30 per cent. Medical management has a mortality over 40 per cent, and, furthermore, treatment with antihypertensive drugs is contraindicated when the dissection compromises critical vessels, such as the coronary, brachiocephalic or renal arteries.24 Aortography is desirable for either course, to locate the site of dissection for the surgeon, or to confirm the patency of important branches for the physician. Retrograde catheterization is now generally accepted as the most efficient method for studying these patients.13,32

#### SUMMARY AND CONCLUSIONS

We have reviewed the angiographic findings in 288 patients with potential surgical diseases of the abdominal aorta. We find that serial aortography, carefully performed, is safe and accurate. Retrograde femoral catheterization is preferred when feasible.

In occlusive disease, the aortogram pre-

cisely identifies the obstructed segment, and shows the condition of collateral and runoff vessels. In aortic stenosis, the measurement of a pressure gradient is a valuable addition in interpreting the significance of lesions roentgenographically shown. Postoperatively, the aortogram permits early detection of complications.

In patients with aneurysms, the size, shape and location of the lesion, and the condition of other arteries shown by arteriography help make the decision whether to operate in borderline cases. Diffuse ectasia can readily be differentiated from aneurysm. When a leaking aneurysm is suspected, an emergency aortography is indicated if the patient is not in shock.

The freer use of arteriography in aortic disease helps in planning surgery or medical management, and also permits us to learn more about the disease processes to improve our future judgment.

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## A SIX CHAMBERED HEART: BIVENTRICULAR OUTLET OBSTRUCTION IN ASSOCIATION WITH INTERVENTRICULAR SEPTAL DEFECT\*

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A CONGENITAL defect of the interventricular septum is one of the commonest developmental anomalies of the heart. When isolated, the clinical and roentgenologic diagnoses generally do not offer any difficulty. On the other hand, it is frequently associated with a spectrum of other congenital anomalies, which have to be identified correctly for diagnostic and therapeutic purposes.

The present case report is that of a very unusual form of congenital biventricular obstruction in association with a ventricular septal defect. The roentgenologic diagnosis was made preoperatively and confirmed by the findings at the time of surgery.

#### REPORT OF A CASE

L.H. was a 16 year old girl when admitted at Boston City Hospital for cardiac catheterization in September 1968. She was known to have a heart murmur since her newborn period. Questionable cyanosis was noted in infancy. Her growth rate was rather slow during infancy and early childhood.

Cardiac catheterization at the age of 7 years demonstrated a left-to-right shunting ventricular septal defect with a 1.9/1.0 pulmonary to systemic flow. Also, a systolic gradient of 50 mm. Hg was recorded between the right ventricle and the pulmonary artery.

The patient remained asymptomatic except for mild premature fatigue on vigorous exertion at the time of her second catheterization. On examination, she had a loud harsh pansystolic murmur along the lower left sternal border

associated with a thrill. The murmur had an ejection quality in the upper left sternal border. The second sound was split along the left sternal border and the second pulmonic sound was of normal intensity. Pulses and blood pressure

The electrocardiogram revealed right axis deviation, incomplete right bundle branch block and combined ventricular hypertrophy. A cardiac series showed a mild degree of biventricular enlargement, pulmonary vascularity in the upper limits of normal and a slightly dilated ascending aorta (Fig. 1, A and B).

The patient underwent cardiac catheterization on September 26, 1968 and the following data were obtained:

$O_2$ Per Cent			
Site	Saturation	Pressure (mm. Hg)	
IVC	76		
SVC	69		
RA	75	4	
RV inflow	75-81	124/10	
RV outflow	84	25/7	
Main PA	83	25/2	
Wedge PA		9	
LV inflow	97	206/12	
LV outflow	97	124/10	
Ascending aort	a 97	124/86	
Pulmonary flow = $6.5 \text{ l./min./m.}^2$			

Systemic flow =  $4.3 \text{ l./min./m.}^2$ Pulmonary/Systemic flow = 1.5/1.0

The examination was completed with selective right and left ventricular angiocardiographies. The right ventricle was approached with a No. 8 NIH catheter introduced through the right saphenous vein. A No. 7 Gensini catheter, using the Seldinger technique through

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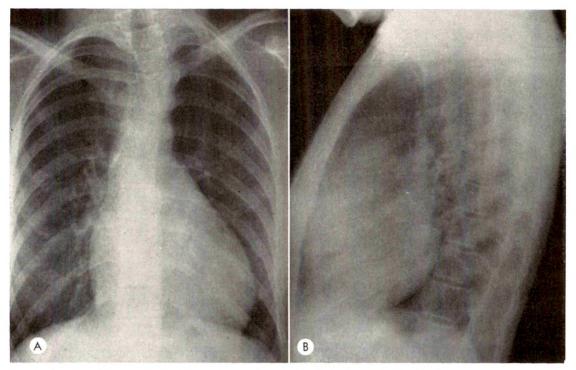


Fig. 1. (A) Frontal and (B) lateral roentgenograms of the chest showing biventricular enlargement and mild increase of the pulmonary vasculature. The ascending aorta is prominent in the frontal projection. (Apparent rotation of the clavicles is due to scoliosis.)

the right femoral artery, was used for the subvalvular aortic injection in the left ventricle: 40 and 30 ml. of renovist was used in the right and left injections, respectively. Rapid serial exposures were done in a biplane programming.

The right ventricular angiocardiograms showed (Fig. 2, A-C): Prominent trabeculation of the right ventricle with a persistent narrowing of the low infundibulum in each systole; shunting of contrast material from the right into the left ventricular outflow; normal crista supraventricularis, pulmonic valve, central and peripheral pulmonary arteries. The pulmonary veins connected with the left atrium in a normal fashion. In the levo phase, the left ventricle showed mild hypertrophy and an abnormal radiolucent line crossed its outflow just below the aortic valve. The ascending aorta was moderately dilated.

The left ventricular angiocardiograms (Fig. 3, A and B) confirmed the presence of a thin membrane crossing the outflow of the left ventricle, about 2 cm. below the aortic valve. There was shunting of contrast material from this "chamber" into the post-stenotic "chamber" of the right ventricle through a septal defect.

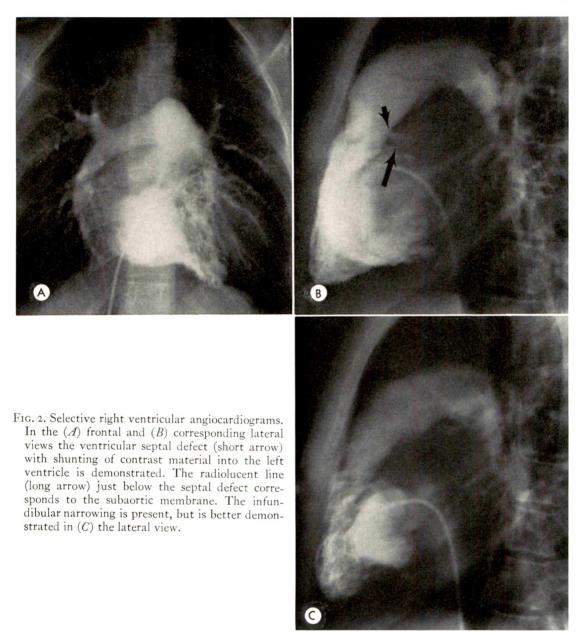
In conclusion, the angiocardiographic diagnosis was: Interventricular septal defect with bidirectional shunting, but mainly left-to-right; membranous subaortic stenosis; and hypertrophic stenosis of the right ventricle.

Under total cardiopulmonary bypass, complete surgical correction was performed on January 22, 1969. A 2 cm. wide muscle band crossing the right ventricular cavity was seen arising as a common trunk from the crista supraventricularis and adjacent ventricular septum. From here this band separated into two limbs, one attached to the anterior wall and the other to the base of the anterior papillary muscle. About 1.5 cm. below the aortic valve, there was a diaphragm with an aperture about 0.5 cm.<sup>2</sup>. Between the aortic valve and the diaphragm, there was a defect in the ventricular septum measuring about 8 mm. in diameter.

The patient had an uneventful recovery after surgery and she is still in satisfactory condition.

#### DISCUSSION

Due to the anatomic characteristics of

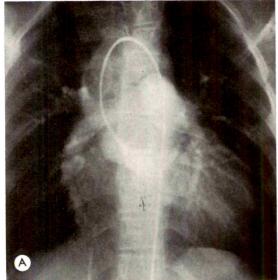


the heart in the present case, this organ was divided into 6 different chambers from a hemodynamic point of view: the 2 atria, the 2 pre-stenotic ventricular segments, and the 2 post-stenotic or pre-valvular ventricular segments.

The clinical signs and symptoms, as well as the data obtained during catheterization, correlate very well with the angiocardiographic and surgical findings. Obviously, the main problem of the case was

at the ventricular level where the prestenotic segments represented the higher pressure chambers. On the other hand, the high interventricular septal defect was communicating with the post-stenotic chambers and consequently the hemodynamic results were not as significant as in the common cases of interventricular septal defects.

In reviewing the literature we have not found any reported case like the present



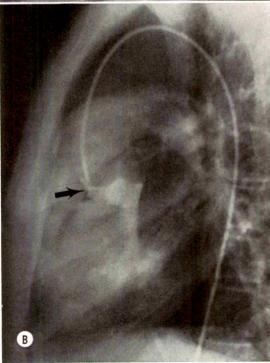


Fig. 3. Selective left ventricular angiocardiograms. (A) The frontal and (B) the lateral projections demonstrate subaortic to subpulmonic shunting of contrast material (arrow). The distorted configuration of the left ventricular outflow, as well as the dilatation of the ascending aorta were also seen in the levo-phase of the right ventricular injection.

one that has been diagnosed by angiocardiography before surgery. Lauer et al.<sup>3</sup> studied 722 hearts with congenital malformations and found only 10 cases of ventricular septal defect with obstruction of the left ventricular outflow, in spite of the fact that ventricular septal defect alone or as a complex was the commonest single lesion. They described a case of a 13 year old girl, who at surgery was found to have infundibular stenosis of the right ventricle, a subaortic membrane and a small ventricular septal defect behind the crista supraventricularis. This is the only case which exhibits quite similar findings to our patient.

Combined congenital aortic and pulmonic stenosis is relatively rare. Steinberg and Holswade<sup>4</sup> reported I case and reviewed the literature which had recorded only II cases until 1967, including the above mentioned case of Lauer *et al.* Obstruction to the ventricular output is the common denominator in all these cases. The anatomic cause may be: (1) inside the outflow of both ventricles (most common form); (2) involving the aortic and pulmonic valves; and (3) combination of one or both ventricular outflows, and one or both valves.

On analyzing the individual ventricular anomalies of our patient, it is interesting to note that there is a high incidence of ventricular septal defect associated with obstructing aberrant muscular bands inside the right ventricle. Hartmann *et al.*<sup>2</sup> reported 3 cases with this pathology and mentioned 15 cases from the literature. In only 2 of these 18 cases a ventricular septal defect was not present.

On the other hand, Baltaxe et al.<sup>1</sup> in a recent review of 24 cases of membranous subaortic stenosis found, among other associated anomalies, 5 cases with a ventricular septal defect. These defects were small in size and located between the aortic valve and the subaortic membrane. Dilatation of the ascending aorta, which was demonstrated in our patient, is also discussed by the authors who emphasize that this associated finding is not as frequent as it has been thought to be in the presence of discrete membranous obstruction.

#### SUMMARY

The case of a 16 year old girl with clinical, angiocardiographic and surgical diagnosis of biventricular outflow obstruction and ventricular septal defect is reported.

The pathologic and hemodynamic features of this uncommon congenital cardiac anomaly are discussed on the basis of the current literature.

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# SHUNTING VIA A DIVERTICULUM OF THE MEMBRANOUS PORTION OF THE VENTRICULAR SEPTUM\*

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TENTRICULAR septal defect as a single lesion is a common form of congenital heart disease. Aneurysms of the membranous septum are relatively rare lesions, especially if a defect is present producing a left-to-right shunt. It has been reported that aneurysms may produce serious hemodynamic changes by obstructing the outflow tract of the right ventricle. The aneurysm will usually project into the right ventricle and can involve the tricuspid valve. As in ventricular septal defects in general, diverticula of the ventricular septum with a defect will cause symptoms, depending on the size of the defect, which may be merely a few millimeters or considerably larger. Diverticula found in the membranous portion of the septum are most common just beneath the aortic valve. It is uncommon to find either a diverticulum or a ventricular septal defect in the lower part of the septum, i.e., muscular portion. There is no clinical picture that is characteristic or even suggestive of a diverticulum with a defect. The symptom's are dependent on the severity of the accompanying ventricular septal defect or other cardiac abnormality. Demonstration of the diverticula can only by accomplished with angiocardiography.

#### ANATOMY AND PATHOLOGY

Ventricular septal defects are most commonly seen in the membranous portion of the ventricular septum. The membranous septum is the thin, easily transilluminated portion of the septum which extends from the rim of the thicker muscular septum upwards to the base of the heart in a close relationship to the aortic and atrioventricular valves. "An aneurysm of the membranous septum may project, therefore, into the right atrium, into the septal leaflet of the tricuspid valve or into the right ventricle." Diverticula of the membranous septum with defects usually have narrow origins which are clearly defined as are diverticula, for example, in the colon.

#### **ETIOLOGY**

The etiology and development of aneurysm or diverticulum of the membranous ventricular septum have been extensively reviewed.1-7 Uncomplicated aneurysms are commonly considered congenital in origin, others have considered aneurysm secondary to endocarditis. Membranous aneurysms have been attributed to trauma. Recently, aneurysm of the membranous portion of the septum has been related to natural spontaneous closure of ventricular septal defects.1,8,7 Spontaneous closure of ventricular septal defects has been reported by various authors. Recently a spontaneous closure of a ventricular septal defect via aneurysm formation has been proven.4 Three cases have been reported where a septal diverticulum with a defect was observed on a second study after being absent on the first angiogram. This theory has also been discussed by Pombo et al.

Recently we have observed 3 cases showing diverticula of the membranous septum with defects.

#### REPORT OF CASES

CASE I. A 23 year old man first noted a heart murmur during an Army physical examina-

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tion. Mild symptoms of fatigue on exertion had caused him to recently change occupation. There was no history of cyanosis, pulmonary infection or familial congenital heart disease. Physical examination revealed a slender male in no distress with no cyanosis or clubbing. The neck veins were not distended. The lungs were clear. Examination of the heart revealed an apex beat at the fifth interspace just lateral to the midclavicular line. No thrill or right ventricular heave was felt. There was an increased P2. A Grade IV systolic murmur, loudest in the third and fourth interspace just left of the sternal border, was present. No diastolic murmur was present. Electrocardiography revealed right axis deviation.

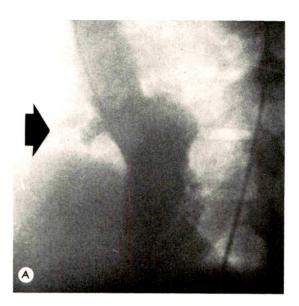
Right and left heart catheterization was performed. The dye dilution curve suggested a small left-to-right shunt. No other hemodynamic abnormalities were noted in the right or left heart.

Left ventricular cineangiography showed a small diverticulum of the membranous portion of the septum with a small fistulous tract into the right ventricle. Minimal left-to-right shunting could be visualized (Fig. 1, A and B).

CASE II. An II year old girl was noted to have a heart murmur and occasional cyanosis at the age of 2 years. At the age of 4 years, cardiac catheterization showed a ventricular septal defect and mild pulmonic stenosis. Since then, she has been asymptomatic with normal growth and development. Physical examination at the time of our study revealed a slender girl with alternating esotropia. There was a prominence of the upper sternum, a palpably increased right ventricular impulse and a faint systolic thrill at the third interspace left sternal border. A Grade III harsh pansystolic murmur was loudest in the mid left sternal border. No diastolic murmur was present. Electrocardiography showed probable right atrial hypertrophy.

Right and left heart catheterization was performed. A small left-to-right shunt was suggested by a dye dilution curve but was not apparent on an oxygen series. Right and left heart pressures were all normal with no evidence of a pulmonic stenosis.

Left ventricle cineangiography showed a diverticulum protruding from the membranous septum into the right ventricle. A small amount of contrast material could be seen passing into



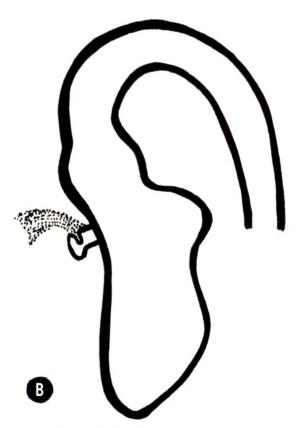
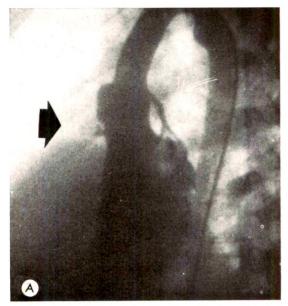


Fig. 1. Case 1. (A) Left ventricular cineangiogram shows a small diverticulum of the membranous portion of the septum with a small fistulous tract into the right ventricle. Minimal left-to-right shunting can be visualized (arrow). (B) Diagram of left ventricular cineangiogram.



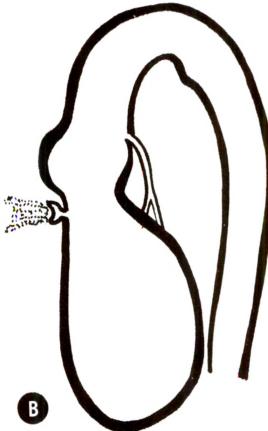


Fig. 2. Case II. (A) Left ventricle cineangiogram showing a diverticulum protruding from the membranous septum into the right ventricle. A small amount of contrast material can be seen passing into the right ventricle through a defect in the

the right ventricle through a defect in the diverticulum (Fig. 2, A and B).

Case III. A 33 year old man was said to have had acute rheumatic fever at the ages of 2 and 5 years. Since that time, he has had a heart murmur, has restricted his activity and was rejected from the Armed Forces.

Physical examination revealed a healthy-appearing man. There was a slight right ventricular lift without a thrill. The heart was not enlarged. There was a Grade IV holosystolic murmur maximal in the fourth left intercostal space. Electrocardiography was normal. A chest roentgenogram was normal.

Right and left heart catheterization was performed. Intracardiac pressures were all normal. A dye dilution curve revealed a 1.5:1 left-to-right shunt which was localized by the oxygen series at the ventricular level.

Selective left ventricular cineangiography demonstrated a small diverticulum high in the membranous portion of the ventricular septum. Contrast material was seen to pass into the right ventricle (Fig. 3,  $\mathcal{A}$  and  $\mathcal{B}$ ).

#### DISCUSSION

There is no specific clinical picture or diagnostic finding to suggest that a diverticulum will be present in association with a ventricular septal defect. In our 3 patients this entity was not suspected prior to cardiac catheterization for a ventricular septal defect. The correct anatomic diagnosis can only be accomplished with selective left ventricular cineangiography in the left anterior oblique position for an optimal view of the septum.

The presence of a diverticulum per se does not affect the treatment, which is dependent upon such factors as the clinical symptoms, the size of the shunt and the presence of pulmonary hypertension. The association of a small ventricular defect with a diverticulum or aneurysm is probably not common. The patients reported above all showed ventricular septal defects associated with small aneurysms in the shape of diverticula. The contrast material

diverticulum (arrow). (B) Diagram of left ventricular cineangiogram.



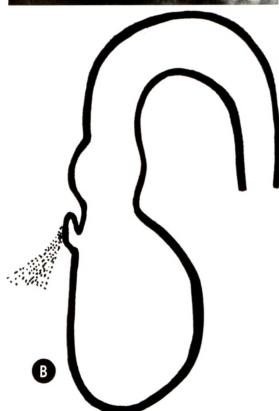


Fig. 3. Case III. (A) Selective left ventricular cineangiogram demonstrates a small diverticulum high in the membranous portion of the ventricular septum. Contrast material is seen to pass into the right

was seen issuing either from the base, sides or tip of the diverticulum-like aneurysm. Comments on etiology have varied from congenital defects, trauma, infection and finally the proven cases of closing ventricular septum with the development of a diverticulum in the closing process.

#### SUMMARY

Three cases of diverticulum of the membranous ventricular septum associated with a ventricular septal defect are reported.

Spontaneous closure of ventricular septal defects via diverticulum formation has been recently proven.

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ventricle (arrow). (B) Diagram of left ventricular cineangiogram.

# SIMPLIFIED SERIAL CORONARY ARTERIOGRAPHY\*

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RECENT technical advances in selective coronary artery catheterization have permitted multiple injections of contrast material without removing the catheter from the orifice of the vessel.1 For the first time, direct serial films as well as cine films can safely be obtained. Judkins recommends a series of cine and serial films which involves 4 sequential rotations of the patient while shifting the table-top in its longitudinal axis from image intensifier to film changer and back.1 With a well-trained team, these maneuvers can be performed in less than 5 minutes, obtaining cine runs in 2, and serial films in 3 projections. A rearrangement of the equipment and a change in positioning of the patient can simplify the sequence of filming and reduce the time required even further.

Rotating cradles permit rapid and continuous change in position of the patient during cine coronary arteriography. These devices are not yet suitable for serial roent-genography because excessive separation of the patient from the film changer produces undesirable geometric unsharpness. In addition, the existing structural supports interfere with horizontal beam roentgenography. Newer cradle designs may improve upon these unsatisfactory features.

In most angiographic units, the film changer is located at one end of the table to permit conventional vertical beam filming. Cine filming is performed in a central location. This combination requires considerable longitudinal table-top motion when shifting from cine or fluoroscopy to serial roentgenography. When filming is performed with a horizontal roentgen-ray beam, as in the Judkins technique, this amount of table-top motion is unnecessary. By placing the lateral film changer‡ in the same transverse plane as the image intensi-

fier, table-top motion is virtually eliminated (Fig. 1). Alignment of the horizontally directed roentgen-ray tube with the film changer is preset either mechanically or with microswitches.

#### TECHNIQUE

We have simplified Judkins' sequence of filming. After transfemoral catheter insertion, the patient is placed in a right posterior oblique position to the table-top. Catheterization of each coronary artery is performed in this position, with the patient centered under the intensifier. The first cine filming is done immediately thereafter, producing a left anterior oblique projection. Without changing the patient's position, the table is moved against the lateral film changer and serial exposures are made, producing a left posterior oblique projection. This projection is equivalent to the right anterior oblique advocated by Judkins and requires considerably less patient motion to achieve. The patient then lies flat on the table and left lateral serial films are exposed. The patient's right side is elevated 20° and an injection is made, which produces a 70° left anterior oblique projection on serial films. Without changing position, the patient is recentered under the image intensifier by a small lateral movement of the table-top and the final cine exposures are made in the right anterior oblique projection.

This sequence produces left and right anterior oblique cine films and serial films with a horizontal roentgen-ray beam in the left lateral, left posterior, and left anterior oblique projections. All 5 projections are achieved with 2 simple rotations of the pa-

<sup>‡</sup> We have used a Franklin roll film changer, but the Schönander AOT changer can be used equally as well.

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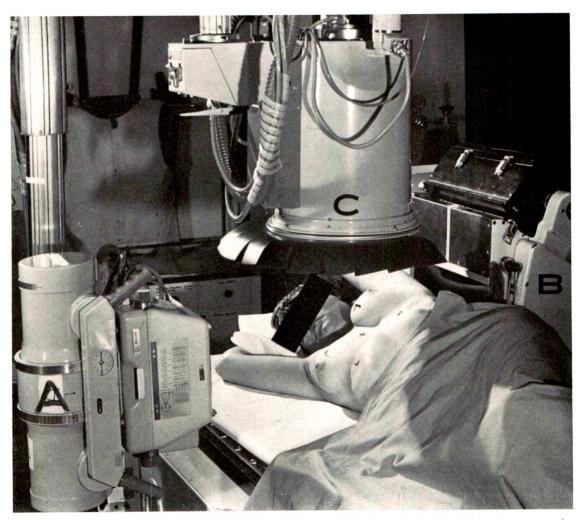


Fig. 1. The patient is positioned for left posterior oblique serial filming. The horizontal roentgen-ray tube (A) and the serial film changer (B) are in the same transverse plane as the image intensifier (C). Only minimal lateral table-top motion is required to shift the patient from serial roentgenography to cinefluoroscopy.

tient and minimal transverse table-top motion. Positioning is performed during the brief time necessary for the characteristic post-injection T wave changes to resolve. The catheter remains in each coronary artery less than 3 minutes while completing the total filming sequence.

#### SUMMARY

A technique is presented which simplifies the sequence of filming in serial coronary angiography. With the method it is possible to obtain cine runs in 2, and serial runs in 3 projections with only 2 simple rotations of the patient and less than 3 minutes of time expended.

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## THE MELTING SIGN IN RESOLVING TRANSIENT **PULMONARY INFARCTION\***

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**D**ULMONARY embolism with or without infarction has been, for many years, a complex diagnostic problem. These complexities have provided a formidable diagnostic challenge to all physicians dealing with pulmonary problems, including the diagnostic radiologist. In a book recently published in the United States, the Section on "The Radiologic Diagnosis of Pulmonary Thromboembolism" is introduced by the following statement:

"The diagnosis of pulmonary thromboembolic disease presents a major problem in the practice of medicine today. In fact, this condition is probably the most misdiagnosed serious disease affecting the cardiovascular system. It is one of the most important causes of, or factors contributing to, unexplained hospital deaths."9

With the potentialities of significant definitive treatment by both medical and surgical means now available, it becomes increasingly imperative that better accuracy be attained in the diagnosis of this common and very important disease process.

Many medical centers, however, can point with justifiable pride to those few case histories of life threatening massive pulmonary embolism which have been successfully treated by pulmonary embolectomy following a diagnostic team effort which has included a "high index of suspicion" by both clinician and radiologist. This, when implemented with modern methods such as radioactive isotopic scanning and pulmonary angiography, has made possible such dramatic therapeutic successes. However, in numbers, the transient pulmonary embolism or infarct which undergoes resolution far exceeds the life threatening variety and many of these continue to escape diagnosis and continue to contribute to patient morbidity.

The transient or resolving infarct of pulmonary embolism is an important entity because, if not recognized and its particular causal pathology not dealt with, recurrence is common and a life threatening episode may later take place.

The authors believe that there is no easy road, no panacea, no superior modality, no single all important finding in recognition of pulmonary embolism and infarction. Rather, the very complexity of the problem should lead us to utilize all available diagnostic parameters and a new one which is being added with this presentation.

Only a cursory recitation of some of the factors which we believe important in the radiologic diagnosis of these conditions will be given, as there is an extensive literature on the subject. First, and perhaps foremost, is the importance of constantly keeping in mind the possibility of pulmonary embolism with or without infarction when dealing with chest problems. The chest physician must remember that the classical symptoms are not infrequently partially or totally absent. The radiologist must remember that the "basal infiltrate" may represent a pulmonary infarction rather than a pneumonia or an area of atelectasis. The monumental contributions of Hampton and Castleman, 10 Westermark, and Fleischner, 5,6 must all be considered: the fact that embolism may exist without in-

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farction; the presence of "Hampton's hump;" the relative avascular region of lung with its increased radiability; and the plump hilus sign. Of greater significance in our hands has been the presence of one or more of the following roent-genographic findings: a hazy focal uniform increased pulmonary density; a minimal unexplained pleural effusion; and slight elevation with indistinctness of the hemi-diaphragm (Figley *et al.*<sup>4</sup>). The important contributions of nuclear medicine and angiography have already been mentioned.

The purpose of this article is to present a roentgenologic observation of one of us (M.E.W.) which for some years has proved. in personal experience, a valuable adjunctive finding in the identification of resolving pulmonary infarction. From a perusal of the radiologic literature, it would appear that not a great deal of research emphasis has been placed on the life history or life cycle of the pulmonary infarct. It has been our observation, when cases of pulmonary infarction have been followed carefully by regular periodic frontal and lateral chest roentgenograms over days and weeks, that most demonstrate a characteristic pattern of resolution. For descriptive purposes we have termed this the melting sign. Its principal use has been the differentiation of resolving pulmonary infarcts and related focal hemorrhagic pulmonary manifestations of the segmental or subsegmental vascular insult from acute inflammatory and infectious disease processes involving the alveolar structure of the lung. The former, for the most part, have shown resolution by a melting or shrinkage in size of the fully attained shadow, its basic configuration, whatever it may be, being maintained. A household analogue would be a periodic viewing of an ice cube after its removal from the refrigerator into an environment of room temperature.

In contradistinction, most inflammatory and infectious infiltrates from which pulmonary infarction would have to be differentiated roentgenographically show a quite different resolution pattern. These

usually demonstrate a gradual patchy resolution or fading away of the roentgenographic density throughout the entire involved area as portrayed on the roentgenogram. The most common example is the resolution of a pneumonia of lobar, segmental or subsegmental distribution. It is a common observation that in standard roentgenographic views pulmonary infarcts present in a variety of configurations, such as: spherical, ovoid, rectangular, band-like, plate-like, or irregular, rather than in the classical triangular or pyramidal, of which only occasional examples are found. The concept of the melting sign is that of gradual reduction in size or shrinkage of the pathologic shadow with the same general configuration seen on the initial roentgenogram being maintained. With respect to the shadow abnormality itself, the resolution is characterized by the resorption of its perimeters with the exception that the infarct usually maintains its pleural base.

On a number of occasions the application of this concentric resolution concept has led to the identification of, and the medical work-up, for pulmonary embolism with infarction when clinical history and physical findings have been sufficiently atypical as to preclude prior diagnosis.

Several illustrative examples of the *melting sign* are presented.

#### ILLUSTRATIVE CASES

Case I. M.M., a 74 year old Caucasian male, presented with history of a cerebral vascular accident 3 weeks prior to admission. He had resulting left hemiparesis. He was transferred from another Los Angeles hospital in a state of mental confusion. His relatives had been told that 2 days previously he had sustained "clots in the lungs." The patient had a history of hypertension for 20 years.

On admission, the patient was afebrile and not dyspneic. A few rales were heard in the left base. His admission chest roentgenogram on March 4, 1969 was an anteroposterior roentgenogram in the sitting position (Fig. 1). It revealed a hazy left lower zone density with adjacent plate-like density and an associated elevation of the left hemidiaphragm. The roent-



Fig. 1. Case I. An anteroposterior chest roentgenogram on admission with the patient in the sitting position. Note the hazy left lower zone density with adjacent plate-like density and an associated elevation of the left hemidiaphragm.

genographic interpretation was consistent with pulmonary embolization and infarction. Periodic follow-up roentgenographic examinations of the chest were carried out on March 12, 1969, March 18, 1969, and March 26, 1969.

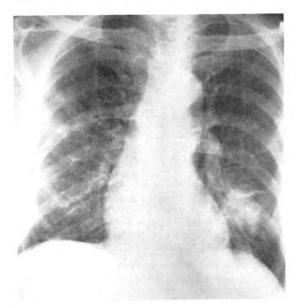


Fig. 2. Case I. Eight days later a repeat posteroanterior chest roentgenogram shows the resolving infarct considerably smaller than on admission. Its basic configuration, however, has been maintained, even when considering the plate-like portion.

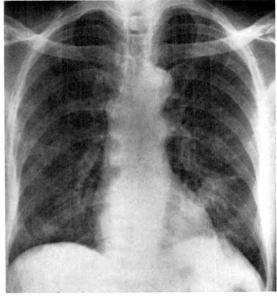


Fig. 3. Case I. Fourteen days after admission, the pulmonary infarct has undergone further "melting."

These (Fig. 2; 3; and 4) demonstrate the resolution pattern of the transient infarct.

During hospitalization, the patient was treated with anticoagulants.

Case II. E.W., a 46 year old Caucasian male, gave a history of rheumatic fever at the age of 20 years. He had noticed slowly progressive exertional dyspnea during the last 5 years.



Fig. 4. Case 1. The appearance of the infarct 22 days after admission.

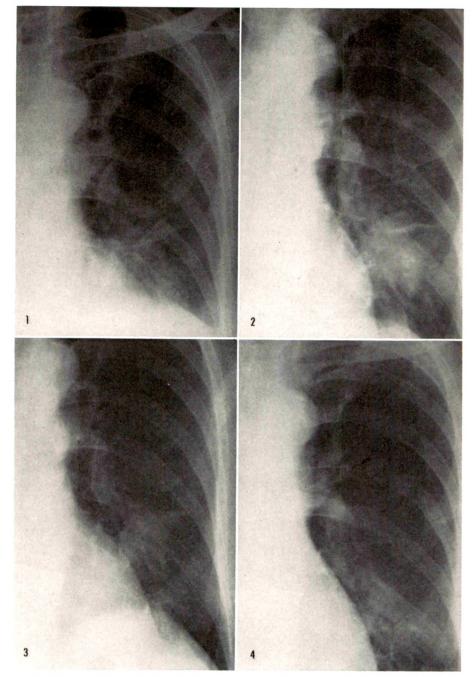


Fig. 1–4. Case I. "Blow-up" photographs of the corresponding roentgenograms in Figures I to 4, respectively. They are presented in this manner so that better detail may be appreciated. Note the "Hampton's hump" in Figure 2.

About a month prior to admission, ankle swelling occurred. Diuretic therapy was administered. A mild persistent cough continued.

The patient was admitted for cardiac workup and catheterization in evaluation for possible open heart surgery. He was in atrial fibrillation with a ventricular rate of 84 per minute. Right and left heart catheterization and angiocardiography established the diagnosis of mitral stenosis and insufficiency, pulmonary hyper-

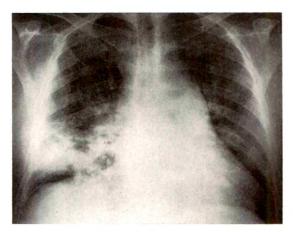


Fig. 5. Case II. A very irregular density is observed in the right lower pulmonary zone on an anteroposterior roentgenogram made 3 days after open heart surgery. The roentgenographic diagnosis was equivocal. The differential diagnosis was primarily a differentiation between pneumonia and pulmonary embolization with infarction.

tension (pulmonary artery pressure 130/53 mm. Hg) and pulmonic valvular insufficiency.

On April 3, 1969, the patient underwent left atrial thrombectomy and mitral valve replacement. The patient was started on coumadin. On April 5, 1969, he developed an oral temperature of 103°F.

On April 6, 1969, chest roentgenogram (Fig. 5) revealed an irregular shadow density in the right lower zone. The roentgenographic diagnosis was equivocal with pneumonia versus pulmonary infarction strongly considered. A repeat examination on April 11, 1969 (Fig. 6) demonstrated the described resolution pattern of a transient pulmonary infarct. A lung scan was immediately obtained and demonstrated an area of decreased perfusion in the anterior inferior portion of the right lung consistent with pulmonary embolus.

Case III. L.R., a 66 year old Caucasian male, was admitted for increasing right exophthalmus, diplopia and disturbed vision which had occurred during the preceding 7 months. Exploration of the right orbit on September 15, 1969 revealed a temporal mass which was biopsied and subsequently diagnosed as lymphosarcoma. The patient developed spiking daily fevers approximately 2 weeks after surgery which continued for 1 month. No radiation therapy or chemotherapy had been instituted.

A chest roentgenogram on October 20, 1969 (Fig. 7A) showed an elevated left hemidiaphragm with a discrete 9 cm. ovoid pleurally based density obliterating the lateral costophrenic sulcus. The findings were considered consistent with pulmonary infarction. Followup chest roentgenograms were obtained on October 23, 1969, November 10, 1969, and December 17, 1969 (Fig. 7, B-D).

Case IV. C.J., M.D., a 56 year old Caucasian male physician, developed pleuritic right lateral thoracic and right shoulder pain after strenuous lifting. The patient had a history of thrombophlebitis 3 years before. The morning after admission, an episode of hemoptysis was reported. Examination revealed moderate left calf tenderness without obvious inflammation.

Chest roentgenogram on March 3, 1969 (Fig. 8) revealed elevation of the right hemidiaphragm with amorphous infiltrate and pleural effusion. The findings were consistent with pulmonary emboli to the right lung. Periodic follow-up roentgenographic examinations of the chest showed gradual resolution of the infarct. Roentgenograms were made on March 4, 1969, March 10, 1969 (Fig. 9), and April 1, 1969 (Fig. 10).

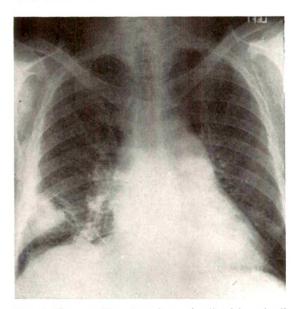


Fig. 6. Case II. Five days later the "melting sign" of resolving transient pulmonary infarction was appreciated. This led to an immediate radioactive isotopic lung scanning with a confirmatory diagnosis of pulmonary embolization.

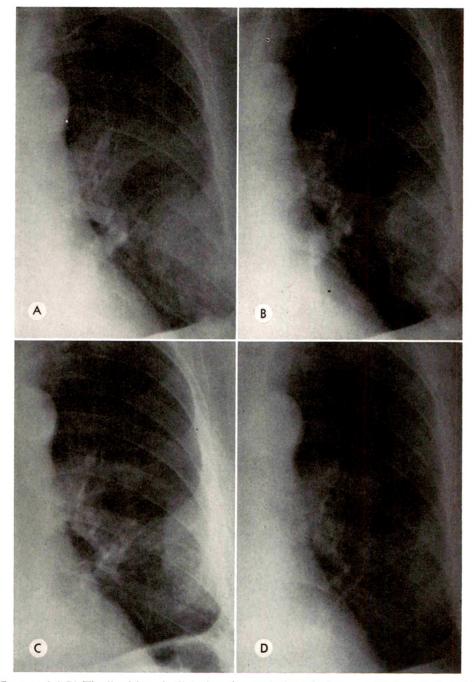


Fig. 7. Case III. (A-D) The "melting sign" during the resolution of a large ovoid pleurally based infarct in the left lung. These are "blow-up" photographs of posteroanterior roentgenograms of the chest made on 10/20/69, 10/23/69, 11/10/69 and 12/17/69. Also note other roentgenographic manifestations of pulmonary embolization: plump hilus, a sharp cut-off of vessel shadows in the lower portion of the hilus, a relative avascular region of lung medial to the infarct with secondary increased radiability, a small pleural reaction, and a laterally located "Hampton's hump."

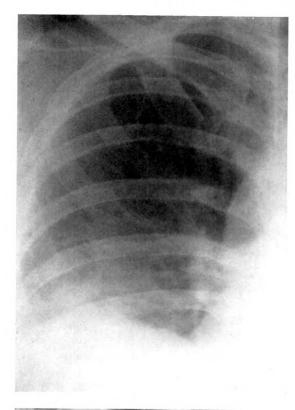




Fig. 8. Case iv. This represents a frequently encountered presentation of pulmonary embolism with infarction: an elevated hemidiaphragm, a hazy focal uniform increased pulmonary density in the base of the lung, and a minimal pleural effusion. This case presented with a classical clinical history, which many times, however, is lacking.



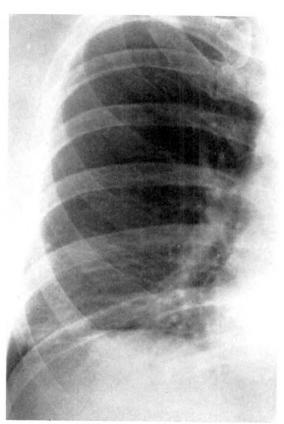


Fig. 10. Case IV. Approximately I month after Figure 8. Further resolution has occurred, but the configuration is remarkably similar to that in Figure 9. The minimal effusion has disappeared.

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Fig. 9. Case IV. One week later the irregular shadow density has melted. Note a minimal pleural effusion which extends into the horizontal fissure.

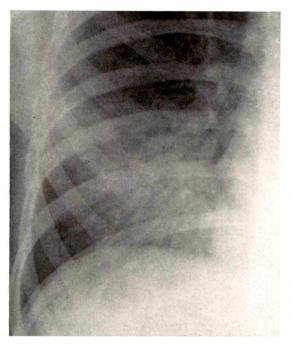


Fig. 11. This is an example of right middle lobe pneumonia from our teaching file.

#### SUMMARY

A new concept of the resolution pattern of a pulmonary infarct as demonstrated on periodic follow-up chest roentgenographic examination is presented. For purposes of simplicity and identification, this concept has been termed the *melting sign*. The concept has been derived by the clinical roentgenologic observation over a number of years that many, if not most, pulmonary infarctions which go to resolution (and do not organize) present a roentgenologic pattern different from resolving pneumonia (Fig. 11; and 12).

The importance of the observation may be stressed by the fact that, in some instances, the sign has been the initial finding leading to the establishment of the diagnosis of pulmonary infarction. Its greater value probably lies in establishing a higher confidence level in the diagnosis of pulmonary thrombo-embolic disease on plain chest roentgenograms when infarction coexists.

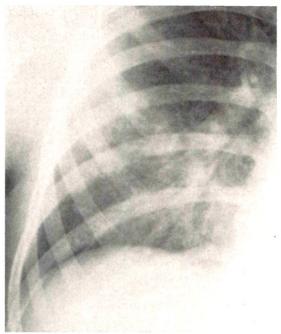


Fig. 12. Two days later, the pneumonia has shown partial resolution. Note that the resolution of pneumonia is patchy and is characterized by a fading of the roentgenographic density throughout the entire involved area. This is in contradistinction to the resolution pattern of most transient pulmonary infarcts as described in this presentation.

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#### INTRAARTERIAL INJECTION OF PROCAINE\*

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THE most common minor complication of retrograde percutaneous arteriography is temporary arterial spasm. The injection of 5-10 ml. of 1 per cent procaine into the artery immediately prior to withdrawal of the catheter, needle, or cannula seems to minimize this postarteriographic arterial spasm. Although this method appears to be successful in reducing or preventing arterial spasm, intravascular injection of procaine may not be void of untoward reactions.

The purpose of this communication is to report our observations in 2 patients who developed symptoms of cortical irritation following the intraarterial injection of 5 ml, of 1 per cent procaine immediately prior to withdrawal of the catheter at the conclusion of percutaneous transaxillary arteriography.

#### DISCUSSION

Arterial spasm may occur with any arteriographic procedure. According to Lang, multiple traumatic punctures, poor local anesthesia, traumatic advancement of the guide wire or catheter, and excessively long catheterization procedures appear to be the most common causes for temporary arterial spasm. Spasm also appears to occur more frequently with brachial and axillary arterial punctures. Curry and Howland<sup>2</sup> observed an incidence of 8 per cent of transient but disturbing arterial spasm following percutaneous brachial-axillary arterial studies. To minimize arterial spasm, they have recommended the routine injection of 5-10 ml. of 1 per cent procaine into the extremity artery at the puncture site immediately prior to removal of the arterial catheter or cannula. Using this method, in a continued series of 215 arteriographies,

they reported no clinical evidence of arterial spasm in the extremity subjected to arterial puncture. Wense<sup>5</sup> also recommended the injection of 10 ml. of 1 per cent procaine intraarterially prior to lumbar aortography in order to minimize arterial spasm. Brehn et al.<sup>1</sup> usually inject 2 ml. of 1 per cent procaine into the carotid artery via needle prior to arteriography in order to alleviate arterial spasm related to injection of contrast media.

The exact mechanism of action of intravascular injection of procaine in minimizing or preventing arterial spasm is unknown. One possible explanation is the analgesic action of procaine directly on the arterioles and capillaries causing widespread vasodilatation.<sup>3,5</sup>

Procaine is rapidly hydrolyzed and its toxicity is relatively low. However, after rapid intravascular administration, this rapid hydrolysis still may not be adequate to prevent accumulation of dangerous levels of procaine in the blood and vital tissues. Procaine diffuses quickly from the blood stream and may develop toxic concentration in extravascular tissues. Restlessness, apprehension, tremors, confusion, delirium, and convulsion may develop in quick succession.

The toxic reactions of intravascular injection of procaine depend on the total dose administered, speed of injection, and concentration of the solution used. We routinely inject 5 ml. of 1 per cent procaine intraarterially immediately prior to the withdrawal of the catheter in all our percutaneous transaxillary arteriographies. We consider this dose and concentration of procaine to be safe (50–100 mg. procaine). Brehn et al.¹ found that for preventing or relieving arterial spasm, 200 mg. of 1 per

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cent procaine can be injected into the carotid artery without serious consequences.

We now believe that the speed of injection is most important and highly influences the dosage effects of intravascular procaine. In the series of 1∞ patients studied by Brehn et al.,¹ 10 per cent developed cortical irritation manifested by simple contralateral extremity spasticity to marked convulsive movements. However, all of these patients were examined under general anesthesia. In their study, there was also no mention about the rate of the intravascular injection of procaine.

Recently, we have observed transient, but alarming cerebral reaction in 2 patients following rapid intraarterial injection of 5 ml. of 1 per cent procaine immediately prior to the withdrawal of the catheter. Both patients had undergone a left transaxillary approach for an antegrade abdominal aortography and bilateral ileofemoral run-off. The duration of the entire procedure in each patient lasted about 1 hour. Both patients suddenly developed mental confusion and black-out spells lasting for less than 1 minute following the inadvertent rapid injection.

Before completely removing the angiographic catheters, we now get another one of the same length and hold it along side the intraarterial catheter as it is withdrawn. This tells us when the tip of the intraarterial catheter has been pulled close to the puncture site. The procaine injection is then started and thereby made extremely close to the exact arterial entry area. The procaine is injected slowly as the catheter is completely withdrawn. Using this method we have had no complication of arterial spasm.

We believe that the rapid injection of the procaine from the axillary artery allowed a significant amount to reach the cerebral circulation, since procaine can diffuse very fast and accumulate in dangerous levels within the brain substance from a rapid intraarterial injection. Although the symp-

toms of cortical irritation experienced by these patients were only transient and relatively mild, still it was alarming to both the patient and the angiographer. These untoward reactions can be avoided if the angiographer injects the procaine slowly just prior to removal of the catheter tip from the axillary artery puncture site. This avoids antegrade and retrograde flow of procaine into the cerebral circulation.

#### SUMMARY

In angiographic procedures, intraarterial injection of 5–10 ml. of 1 per cent procaine has been extensively used prior to withdrawal of the catheter, needle, or cannula in order to minimize arterial spasm. However, the angiographer must be aware of the possibility of cortical irritation if the procaine is injected rapidly. The symptoms are transient, but nevertheless alarming to both the patient and the angiographer.

We report 2 patients who had percutaneous transaxillary arteriography, each of whom developed transient symptoms of marked cortical irritation following the rapid intravascular injection of 5 ml. of 1 per cent procaine just prior to the removal of the catheter.

We believe that careful attention to slow injection quite near the arterial entry site will avoid such cortical irritation. To our knowledge this minor, but possibly major, complication has not been reported previously.

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### PHLEBOGRAPHIC TECHNIQUES IN THE DIAGNOSIS OF ACUTE DEEP VENOUS THROMBOSIS OF THE LOWER LIMB\*

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CLINICAL examination for acute deep venous thrombosis results in an over-diagnosis of about 50 per cent of all cases. <sup>5,9</sup> Such overdiagnosis can be avoided by the use of phlebography, which is simple, safe and reliable. <sup>1-4,6,7,10</sup> However, many radiologists are unaware of the value of phlebography in the diagnosis of acute leg thrombosis, and others feel that the technical performance of the examination is difficult and the appearance of the phlebograms elusive.

This paper describes some phlebographic techniques for diagnosing acute deep venous thrombosis of the leg. They are based on the examination of more than 300 cases of phlebographically diagnosed acute deep venous leg thrombosis.

#### DEEP VENOUS THROMBOSIS OF THE LOWER LEG VEINS

The veins of the lower leg are examined as follows: With the patient sitting on the end of an ordinary roentgenographic table, with the lower leg vertical and the foot resting on a stool, 40 ml. of 60 per cent contrast medium is injected into a dorsal foot vein, preferably the dorsal vein of the great toe. No tourniquet is used to obtain any selective distribution of the contrast medium to the deep veins. Frontal and lateral roentgenograms of the lower leg are obtained before and after the end of the injection. The patient is afterwards placed supine and the leg is raised to accelerate the flow of contrast medium out of the leg veins.

A thrombosis confined to the deep crural veins results in phlebitis with edema of the surrounding soft tissue. This in turn increases the subfascial soft tissue pressure in the calf. As the crural fascia is fairly inelastic, even moderate subfascial edema is sufficient to raise the subfascial pressure above the venous pressure of the leg. This prevents the contrast medium injected into the venous system of the foot from flowing centripetally via the deep crural veins, because these veins pass through the subfascial high pressure area.<sup>8</sup> (In normals both the deep and the superficial crural veins are well filled with contrast medium by the phlebographic technique used [Fig. 1].)

Owing to the increase in subfascial pressure, the contrast medium by-passes the deep crural veins and flows centripetally via the superficial veins. However, the arterial flow to the calf muscles is less affected by the increased subfascial pressure, and the muscle veins of the calf are supplied with blood from the capillary bed. As the deep veins are obstructed by the thrombosis and/or by the high subfascial pressure, the venous return from the subfascial area cannot flow through the deep crural veins. The perforating veins are therefore distended and venous blood from the subfascial compartment is emptied into the superficial veins. Flow of this non opaque blood into superficial veins filled with contrast medium produces patchy or streamline defects in the phlebograms (Fig. 2). The phlebographic diagnosis of acute lower leg thrombosis is consequently based on the following signs: non-visualization of the deep crural veins; a collateral flow through the superficial crural veins; and patchy or streamline filling defects in the superficial veins.

The superficial veins are slightly dilated and a considerable increase in the velocity

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of the flow in the superficial veins is observed; *i.e.*, signs of overloading of these veins. Judging from our experience the phlebographic pattern described is seen in about 80 per cent of all cases of acute deep lower leg thrombosis. In the remaining



Fig. 1. Ascending phlebogram of lower leg in a patient with acute deep venous thrombosis. There is no contrast medium filling of deep veins.



Fig. 2. Detail of superficial veins in a patient with acute deep lower leg thrombosis. Note streamline and patchy defects in the contrast medium.

cases the phlebitis is not severe enough to raise the subfascial pressure to a level above that of the venous pressure. In these patients the deep crural veins are visualized, and the thrombosis is easily demonstrated as a filling defect in the deep veins (Fig. 3).

### DEEP VENOUS THROMBOSIS OF THE POPLITEAL AND FEMORAL VEINS

Lower leg thrombosis may extend to the more proximal parts of the leg. Deep leg thrombosis may also be confined to the popliteal and femoral veins and thereby not involve the veins of the lower leg. Whatever the extent and localization of the thrombosis, the radiologist must always demonstrate the proximal part of all thrombi. It is necessary to evaluate to what extent the "tail" of the thrombus is floating freely in the deep veins, this condition carrying a considerable risk of embolism. Moreover, it is the appearance of the proximal part of the thrombus that decides the method of treatment in a given case; e.g., thrombectomy, anticoagulants or thrombolytics.

The phlebographic technique differs with the assumed extent of the thrombosis. If the proximal part of the thrombus is con-

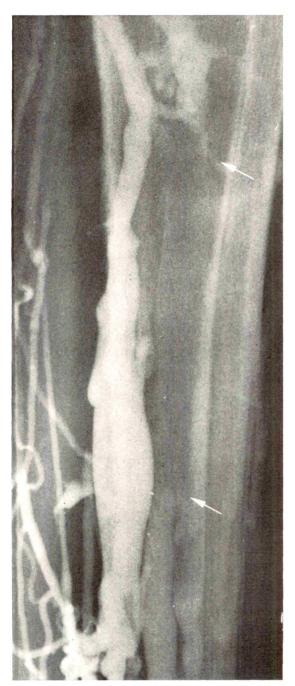


Fig. 3. Lower leg phlebogram in a patient with acute deep thrombosis in the posterior tibial vein.

fined to the popliteal or femoral veins the following method may be useful.

With the patient supine on an ordinary roentgenographic table, the great saphenous vein or one of its branches is punctured at

or just below the level of the knee. A tourniquet is firmly wrapped around the upper thigh to shut off the flow through the great saphenous vein. Contrast medium (40 ml. of a 60 per cent solution) is rapidly injected into the great saphenous system. If the valves of the great saphenous system are incompetent, the superficial veins below the injection needle must be compressed by a second tourniquet. This is necessary to prevent the injected contrast medium from flowing in the retrograde direction of the saphenous system. As the contrast medium cannot escape in either direction in the saphenous system, it is forced into the popliteal vein via the sural perforating veins and into the femoral vein via the perforators at the level of the adductor canal. If there is an interspace between the thrombus and the walls of the vein, or if the thrombus is floating in the lumen of the vein, contrast medium will outline the thrombus, and the thrombus will be demonstrated as a filling defect and the length of its "tail" may be assessed (Fig. 4, A-C). On the other hand, if the thrombus is firmly adherent to the walls of the vein, no contrast medium can be forced into the popliteal and femoral veins (Fig. 5). In such cases the injection increases the pressure in the great saphenous vein to such a degree that the tourniquet around the thigh can no longer prevent the contrast medium from escaping in the central direction. In such cases the proximal part of the thrombus should be sought in the uppermost part of the femoral vein or in the iliac veins. The examination must then be extended to visualize these venous segments.

DEEP VENOUS THROMBOSIS OF THE UPPERMOST PART OF THE FEMORAL VEIN AND OF THE ILIAC VEINS

If the proximal part of the thrombus is confined to the upper part of the femoral vein or to the external or common iliac veins, the following technique can be employed.

It is worth while to try femoral phlebography with percutaneous injection of contrast medium into this vein in the groin.

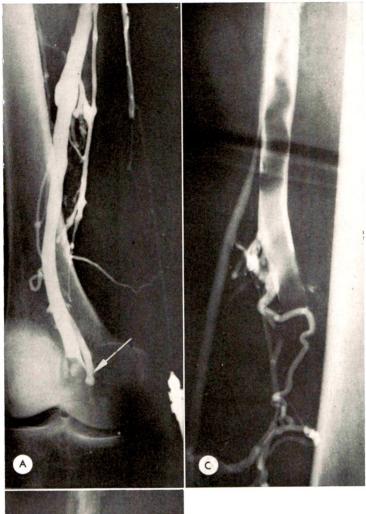




Fig. 4. Lower leg thrombosis with extension in the central direction. (A) The tip of the thrombus is at arrow in the popliteal vein. (B) Floating tip of thrombus at arrows in popliteal vein. (C) Floating thrombus in the femoral vein.

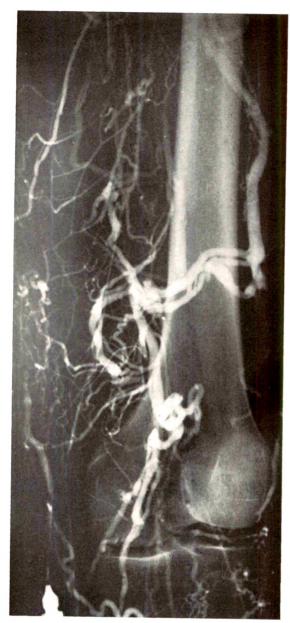


Fig. 5. Thrombosis in the popliteo-femoral veins. Complete occlusion of these veins; no contrast medium can be forced into their lumen.

If the needle is introduced above the tip of the thrombus, a retrograde phlebography—contrast medium injection during straining—may bring the contrast medium injected in the retrograde direction to visualize the proximal part of the thrombus (Fig. 6, A and B).

However, if the thrombosis extends

above the level of the groin, percutaneous puncture of the femoral vein filled with thrombotic masses may be difficult or impossible. If the entire thrombus is adherent to the walls of the vein all puncture trials are futile. But small fragments of a thrombus aspirated with the puncture needle are informative. If the thrombus is floating in the lumen of the vein or is only partially adherent to the walls of the vessel, femoral puncture may be successfully performed. It is often possible to pass a fairly fine needle into the interspace between the thrombus and the wall of the vein.

Injection of 20 ml. contrast medium will visualize the thrombus as a filling defect, varying in size with the mural adhesion and extension of the floating tail of the thrombus (Fig. 7).

An important question is whether this phlebographic technique involves any risk of embolism.

Theoretically, introduction of a needle into a vein with a thrombus loosely attached to the wall carries a risk of embolism. But in none of our cases has phlebographic

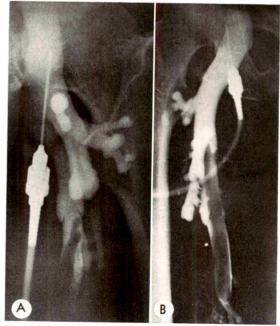


Fig. 6. Retrograde femoral phlebograms. Floating tip of thrombus in the femoral vein. (A) Short and (B) long floating portion of the thrombus.

examination ever been complicated by such embolism.

If a thrombus occludes the femoral vein and direct femoral phlebography cannot be performed, another phlebographic tech-

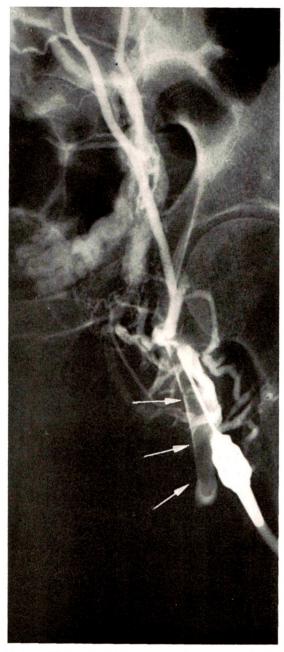


Fig. 7. Femoral phlebogram. Injection needle introduced into the space between the thrombus and the wall of the vein. At arrows, partial outlining of the thrombus.

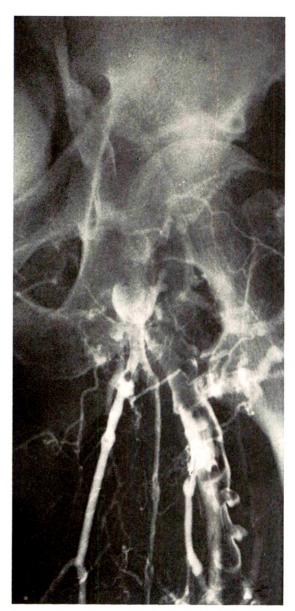


Fig. 8. Contrast medium injection into superficial vein in the groin. Note thrombotic masses in the femoral and deep femoral veins.

nique may be used. When the venous return from the leg via the femoral vein is occluded by a thrombus, the superficial veins of the groin are dilated, because they then serve as collaterals to the deep vein. One of the dilated superficial veins is punctured by a fine needle and 20 ml. of contrast medium is injected. This visualizes the collaterals, but a small amount of the con-

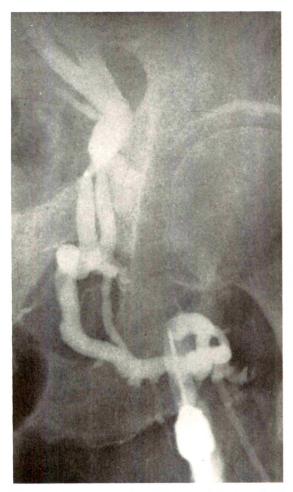


Fig. 9. Contrast medium injection into superficial vein in the groin. The medium flows centrally via the obturator and internal iliac veins.

trast medium may be forced into the femoral vein and fill a narrow lumen between the thrombus and the venous wall (Fig. 8). If it does not, the collateral pathways will yield valuable information on the extent of the thrombosis.

If the contrast medium from the groin flows via the obturator and internal iliac veins to the common iliac vein, the tip of the thrombus is located in the external iliac vein (Fig. 9). If the contrast medium flows via prepubic collaterals to the contralateral groin, the tip of the thrombus lies within the common iliac vein. Finally, if the contrast medium is distributed to the

veins of the abdominal wall, the thrombotic process has probably occluded the lower part of the inferior caval vein.

The slightest suspicion of thrombotic

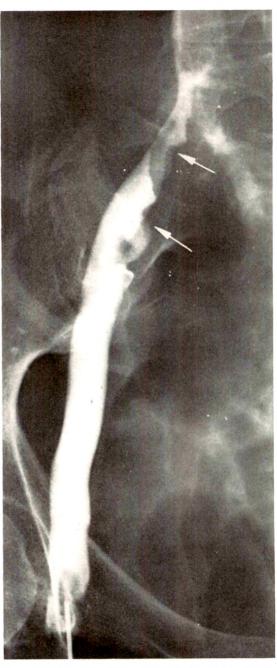


Fig. 10. Femoral phlebogram of the right side in a case with acute thrombosis of the left leg. At arrows thrombotic masses in the confluence region of the iliac and inferior caval veins are present.

involvement of the inferior caval vein is an absolute indication for cavography from the contralateral side. In this examination contrast medium is injected into the femoral vein of the healthy leg, without the patient straining, to visualize the inferior part of the caval vein (Fig. 10).

#### CONCLUSION

Leg thrombosis may imply a life threatening risk of embolism. Its sequel is a condition that seriously deteriorates the venous return from the leg. So far, phlebography is the only reliable method for a firm diagnosis of the disease. Clinically suspected thrombosis is therefore an indication for phlebography. Such a phlebography must include the whole leg and must clarify the extent of the thrombosis in the central direction.

#### SUMMARY

The phlebographic diagnosis of deep venous leg thrombosis is described.

Different methods are necessary to demonstrate thromboses of different extent in the deep veins.

The importance of visualization of the proximal part of the thrombosis is stressed.

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## A PHARMACOLOGIC BASIS FOR PERIPHERAL VASCULAR RESISTANCE CHANGES WITH CONTRAST MEDIA INJECTIONS\*

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IT HAS been known for some time that the injection of radiopaque contrast media into the peripheral arterial system will produce a fall in peripheral vascular resistance (PVR) and an increase in flow. It has also been appreciated for some years that the hypertonicity of the contrast media plays some role in this change in peripheral resistance, and that for some compounds there may be additional mechanisms brought into play. 2.6,8,9.11,13 The nature of these mechanisms is unclear and the specific role that the cations may play in hyperosmotic substances should be further elucidated. 1.4,5

The effect of contrast media on neuromuscular function has not been previously studied. Our experiment points to a neuromuscular end plate effect, via cholinergic (parasympathetic) pathways.

#### METHOD

In order to limit the number of variables in the test situation we used an animal model where all changes in peripheral resistance were divorced from central cardio-vascular effects, and wherein flow changes were held constant, in order to fully study subtle changes in peripheral vascular resistance. Partially conditioned mongrel dogs of 15–20 kg. in size were anesthetized with nembutal and maintained on artificial respiration throughout the course of the study. Multiple injections carried out on each of 5 dogs were done for each contrast material before and after each blocking agent studied. All studies were done as

acute experiments and the animal sacrificed at the conclusion.

Blood gasses were monitored and serum pH was maintained between 7.3 and 7.4. The flow from the left femoral artery was diverted via Tygon tubing into a Sigmamotor pump and then infused into the contralateral femoral artery beyond the point of proximal ligature (Fig. 1). In this model when the pump was activated there was little or no collateral flow to the perfused limb (Fig. 2, A and B). In some animals the carotid arteries were exposed to enable us to produce carotid hypotension and, by reflex, an increase in peripheral vascular resistance, thus assuring the integrity of

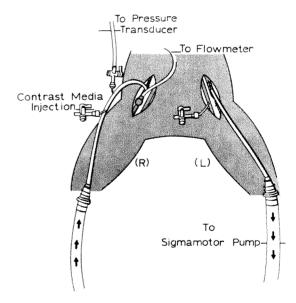


Fig. 1. Flow is diverted from the left femoral artery through a constant flow pump and back into the right femoral artery.

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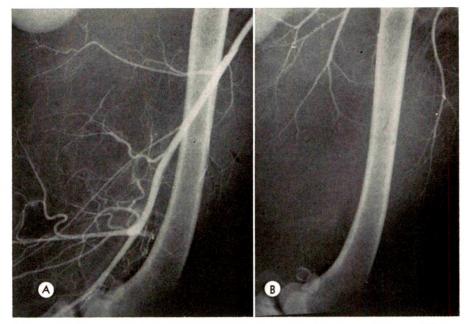


Fig. 2. (A) The vessels are filled by injection into the right femoral artery. (B) An aortic injection with delayed roentgenogram showing no collateral flow.

adrenergic pathways and the alpha receptors.

The design of the experiment entailed the injection of selected contrast media and other substances into the perfused limb to establish the control observations in peripheral vascular resistance. The contrast media injected included the sodium and methylglucamine salts of acetrizoate, diatrizoate, iodipamide, and iothalamate (Table I). Very small quantities were utilized to ensure the sensitivity of the system. In addition, acetylcholine, hypertonic sodium chloride, methylglucamine chloride,

and glucose were injected. Acetylcholine was always injected at a dosage of 50 µg. and all of the other substances were injected in 0.5 ml. quantities in equiosmolar solution to 35 per cent Urokon. In order to examine the mechanism of the induced changes in peripheral vascular resistance, a number of modifying drugs were introduced. These included, atropine—a cholinergic blocker, propranolol—a beta adrenergic blocker, dibenzyline—an alpha adrenergic blocker, and diphenhydramine hydrochloride (Benadryl)—an antihistamine. In addition, some dogs were pre-

#### TABLE I

Sodium Acetrizoate Methylglucamine Acetrizoate	_	Urokon (Mallinckrodt Chemical Works, St. Louis, Missouri)
Sodium Diatrizoate	_	Hypaque (Winthrop Laboratories, N.Y.C.)
Methylglucamine Diatrizoate	_	Renografin (E. R. Squibb & Sons, Inc., New Brunswick, New Jersey)
Sodium Iothalamate Methylglucamine Iothalamate	_	Conray 400 { (Mallinckrodt Chemical Works, Conray 60 { St. Louis, Missouri)
Sodium Iodipamide Methylglucamine Iodipamide	_	Cholografin (E. R. Squibb & Sons, Inc., Cholografin New Brunswick, New Jersey)

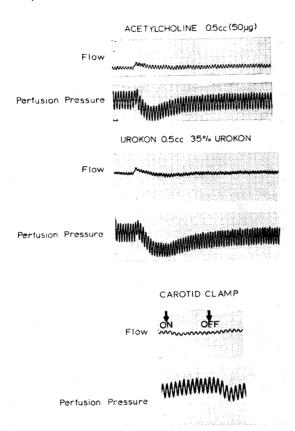


Fig. 3. Characteristic fall in pressure (with controlled flow) following injection of acetylcholine and Urokon, indicating a drop in peripheral vascular resistance. Also seen is the sympathetic reflex following carotid clamping, raising peripheral vascular resistance.

treated with trimethaphan camsylate (Arfonad)—a ganglionic blocker, and some with reserpine—to deplete stored catecholamines.

#### RESULTS

The characteristic change in peripheral vascular resistance after the introduction of sodium acetrizoate can be seen in Figure 3. The similarity to the change with acetylcholine can be seen. Also shown here is the increase in peripheral vascular resistance following carotid clamping, indicating that the reflex from the carotid baroreceptors through the autonomic nerve pathways was intact.

Of the contrast media examined in this study, the greatest change in peripheral

vascular resistance was found with injections of sodium iodipamide. In order of decreasing effect were: meglumine iodipamide, sodium iothalamate, sodium acetrizoate, sodium diatrizoate, meglumine iothalamate, meglumine acetrizoate, and finally meglumine diatrizoate. The response to equiosmolar sodium chloride was approximately the same as that noted with sodium diatrizoate (Fig. 4, A and B). Injections of equiosmolar glucose and of methylglucamine chloride both produced only a minimal change in peripheral vascular resistance, each about 5 per cent before and after atropine. On the whole, the sodium compounds were more reactive than the methylglucamine.

Of the blocking and modifying compounds tested, only atropine altered the response to the injection of 0.5 ml. of the test substances (Fig. 5). Figure 6 illustrates the responses evoked by 10 injections of sodium acetrizoate in 5 dogs and the modification of these responses after the injection of 2 mg./kg. of atropine intravenously.

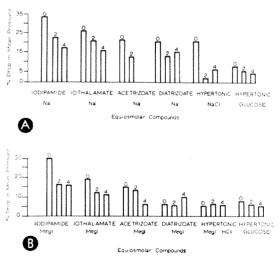


FIG. 4. (A and B) Atropine blockade. Comparison of responses following intraarterial injections of sodium and meglumine compounds and hypertonic saline and glucose. The numbers above each bar represent the number of milligrams per kilogram atropine given before contrast injections. Each bar represents average response from 10 injections in 5 dogs.

For comparison, this figure also shows the response to 50  $\mu$ g. of acetylcholine and the diminution in this response after a similar dose of atropine. Since the duration of the response to the test substances was approximately the same for all contrast media examined, the duration was not factored into the results.

The substitution of normal saline for blood in the perfused limb did not alter the changes of peripheral vascular resistance induced by injections of contrast media. Pretreatment of the animals with an antihistamine did not alter the induced change in resistance. Furthermore, assays for plasma histamine after introduction of contrast media failed to show any evidence of histamine release attributable to contrast media. Bradykinin assays of the venous effluent from the femoral area as well as from other arterial injection sites (kindly carried out by Dr. Kenneth Melmon of the University of California, San Francisco) failed to show any evidence of bradykinin elevations consequent to injections of contrast media. Each of the above were studies limited to 2 or 3 dogs.

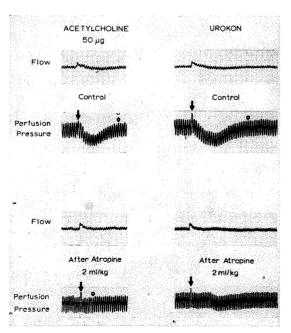


Fig. 5. Similar blockade of contrast medium and acetylcholine by atropine.

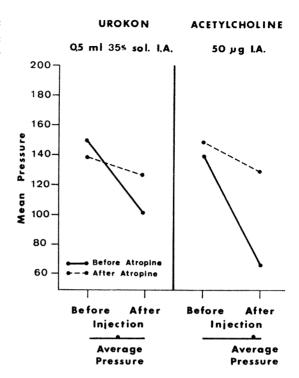


Fig. 6. Summary graph of atropine block of peripheral vascular resistance (PVR) drop induced by acetylcholine or contrast media.

#### DISCUSSION

The changes in vascular resistance following contrast media injections have now been amply documented in numerous arterial beds in investigative animals and in man.<sup>3,6,7,12</sup> In theory, a diminution in peripheral vascular resistance might result from one, or several, of a number of different mechanisms. Some of these are:

- A direct action on smooth muscle cells in the arteries.
- 2. Stimulation of beta adrenergic (or dilating) activity or direct effect on beta adrenergic receptors.
- 3. Selective inhibition of alpha adrenergic (or constricting) receptors.
- 4. Release of histamine and/or activation of histaminic receptors.
- 5. Release of bradykinin.
- 6. Stimulation of cholinergic (gamma) activity or direct effect on cholinergic (or dilating) receptors.

In view of the fact that there was no evi-

dence of histamine release or effect of the antihistamines, and in view of the fact that there was no evidence of release of bradykinin, these humoral substances are unlikely pathogenic factors. Alpha inhibition did not occur, as indicated by persistence of the carotid reflex-constrictor response. Beta blockade did not modify the responses. Since the drugs modifying the vasodilator response involved only the gamma cholinergic receptors, it seems probable that the neurogenic effect of contrast media is mediated via cholinergic pathways. The hypertonic sodium chloride was also blocked by atropine, and it, therefore, seems likely that this effect is also mediated via a cholinergic system. At the same time, note must be taken of the fact that equiosmolar glucose produces some drop in peripheral vascular resistance, although small, and thus, osmotic forces per se also contribute to the change in peripheral vascular pressure. It is impossible to be certain from the evidence presented whether the cholinergic stimulus comes about via an effect on the parasympathetic nerve ending with release of acetylcholine, or a direct effect on the gamma (cholinergic) end plate, or whether cholinesterase inhibition by the contrast media per se plays a role. In light of the fact that the greatest changes in peripheral vascular resistance are seen in association with injections of the contrast media that have been shown by our laboratories to be particularly potent cholinesterase inhibitors, 10 it is possible that this inhibitory mechanism may be invoked. This would allow a local increase in acetylcholine, producing vasodilatation.

#### CONCLUSION

- 1. The drop in peripheral vascular resistance demonstrated after injection of contrast media into the isolated perfused canine hind limb appears to be due to a combination of cholinergic effects, and osmotic effects
- 2. It seems probable that the sodium cation may act chiefly via the production of a similar cholinergic stimulus.

3. Neither histamine, nor bradykinin, nor red blood cells need be present to obtain this vasodilatory effect.

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#### RADIOLOGY OF THE THORACIC DUCT\*

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MOST studies of the thoracic duct have been undertaken on postmortem specimens by gross dissection<sup>26</sup> or by injection of contrast material into the duct.<sup>7,8</sup> The retrograde injection of contrast agent in patients with advanced neoplastic disease<sup>4</sup> and preoperative<sup>6,20</sup> and operative<sup>30</sup> retrograde and prograde duct opacification has been performed. Lymphangiography affords the unique opportunity of evaluating the thoracic duct systematically under nonoperative conditions during life.<sup>22,23,32</sup>

The present study was undertaken to analyze the anatomy, anomalies, and pathologic features of the thoracic duct as seen *in vivo* during lymphangiography.

#### MATERIAL AND METHOD

In 390 sequential lymphangiograms a detailed analysis of the appearance of the thoracic duct was performed. The technique utilized has been described in detail<sup>3</sup> and incorporates anteroposterior and left posterior oblique roentgenograms of the thoracic duct routinely. Other projections were obtained as required. The quality of visualization of the thoracic duct was observed, and the portions of the duct visualized were noted. The presence, position,

Table I
DISTRIBUTION BY TYPE OF DISEASE

Disease	No. of Cases
Hodgkin's disease	152
Reticulum cell sarcoma	47
Lymphosarcoma	58
Carcinoma	77
Other	56
Total	390

TABLE II
DISTRIBUTION BY AGE OF PATIENT

Age (yr.)	No. of Patients				
0-10	8				
I I-20	48				
21-30	68				
31-40	66				
41-50	91				
51-60	56				
61-70	29				
70+	9				
No age	15				
Total	390				

size, and location of the duct in relationship to the spine, carina, and trachea were noted. The diameter of the duct was recorded, as were the presence of obstruction, collateral circulation, displacement, tortuosity, kinking, and nonfilling.

#### RESULTS

The underlying diseases and the age of the patients in the study are indicated in Tables I and II. No relation between age and variation in relative size, position, or any other characteristics of the thoracic duct was apparent. In 348 of the 390 studies the thoracic duct was opacified, and in 232 patients the entire thoracic portion of the duct was filled.

#### THE CISTERNA CHYLI

The thoracic duct originates from two lumbar trunks which collect lymph and contrast material flowing from the lower extremities. The site at which the 2 lumbar trunks unite is the origin of the duct, and the initial prominent confluence is the cisterna chyli.

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Fig. 1. Cisterna chyli. The lumbar trunks have converged to form a localized bulbous dilatation representing the classic appearance of the cisterna chyli. It is situated approximately in the midline at the level of the first and second lumbar vertebrae. Note that not all of the lumbar lymph trunks terminate directly in the cisterna chyli. Others may form the thoracic duct at a higher level. (A) Anteroposterior projection. (B) Right posterior oblique projection. (C) Left posterior oblique projection.

The classical bulbous dilatation of the cisterna chyli was visible in 204 studies or 53 per cent (Fig. 1, A-C). In other cases the caliber of the cisterna chyli was not much larger than that of the thoracic duct (Fig. 2). In many cases a plexus-like origin of the thoracic duct was present with or without ampullar dilatation (Fig. 3; and 4). In these cases the thoracic duct usually started at the level of T-12. Multiple small channels were seen as high as T-11 in 14 cases. In 2 cases both lumbar trunks were dilated terminally, and the thoracic duct originated from the junction of the terminal bulges.

The cisterna chyli was located at the level of T-12 in 74 cases (Fig. 2) and at the L-1 or L-2 levels in 130 cases (Fig. 1, A-C). Usually, it was less than 5 cm. in length (Table III) although in 55 instances it was longer than 5 cm. In 5 cases the length was 7 cm. or greater.

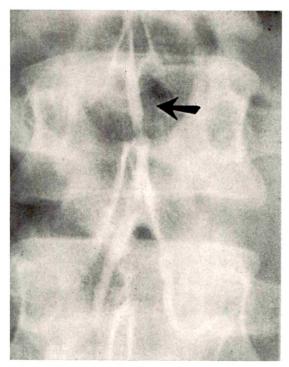


Fig. 2. Cisterna chyli. The continuation of the cisterna chyli with the lumbar lymph trunks is apparent (arrow points to upper portion of cisterna chyli). Its caliber is larger than that of the thoracic duct above but does not have the localized bulbous dilatation that is frequently seen.

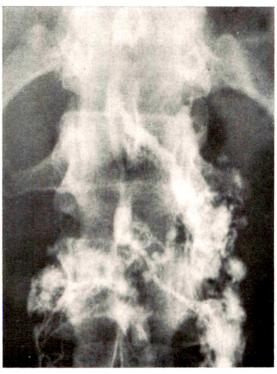


FIG. 3. Cisterna chyli. Rather than arising from 2 major lumbar trunks, the cisterna chyli is a continuation of a plexus-like group of lymphatic ducts joining in the midline at separate levels. Note that the cisterna chyli extends cephalad to the 12th thoracic vertebra.

Its appearance was polymorphic. An inverted "Y" or inverted "V" (Fig. 2), a "rope of pearls," or comma-like configurations (Fig. 1, A–C) were most commonly seen. Consecutive filming demonstrated clear-cut differences in the caliber of the cisterna chyli, which sometimes represented contraction waves when studied by cine fluorography.

#### THE THORACIC DUCT

The thoracic duct is a continuation of the cisterna chyli from its abdominal segment into the thorax, entering through the aortic hiatus of the diaphragm. At its beginning it overlies the spinous processes of the vertebral column<sup>1,25</sup> or is located slightly to the right or left of it (Fig. 3; and 5A) at the level of L-1 to T-12. On rare occasions a left-sided thoracic duct is present, but in the majority of our cases the

duct lay to the right of the aorta and followed its course. Thus, with a tortuous aorta projecting relatively far to the left of the spine, the thoracic duct occupied a position well lateral to the vertebral bodies. In most cases it was slightly to the right of the midline as it entered the thorax and moved to the left of the midline at the level of the 10th to 12th thoracic vertebrae (Fig. 5, B and C). At times it remained in the midline as high as the 5th or 6th thoracic vertebra (Fig. 6); its position seemed related largely to the location of the aorta.

At the carina the thoracic duct crosses the left main stem bronchus and runs parallel but dorsal to the left lateral wall of the trachea. The duct is directed sharply ventrad over the dorsal aspect of the aortic knob at about the level of the 5th or 6th thoracic vertebra to ascend cephalad in close relationship to the trachea (Fig. 7, A and B). It leaves the thorax between the esophagus and the left subclavian artery and runs posterior to the left innominate vein. The upper one-third of the duct, from the tracheal wall to the point of entry into the venous system, resembles an inverted "J" with the most cephalic portion directed to the left (Fig. 8). Much of the cephalic one-third of the thoracic duct is supraclavicular in location and represents the cervical portion of the duct. The terminal 4 cm. was visualized either parallel to the clavicle or forming an arch 2.5 to 3 cm. above the clavicle. Uncommonly it was sagittally oriented and directed laterally and cephalad. It joined the venous system by emptying most commonly into the in-

TABLE III
POSITION AND LENGTH OF CISTERNA CHYLI

	No. of Cases
Position	
Level T-12	74
L-I to L-2	130
Length	
I to 3 cm.	IOI
3 to 5 cm.	48
over 5 cm.	55



Fig. 4. Cisterna chyli. Lateral projection. The localized cluster of lymphatic ducts resembles a lymphocele. Not only the cisterna chyli but also the parallel lymphatic ducts are dilated. Although this appearance is seen with obstruction of the thoracic duct, it may also be seen in normal individuals.

ternal jugular vein, but it also emptied into the subclavian, innominate, and external jugular veins, as well as the junction of internal jugular and subclavian veins.<sup>14</sup>

The maximum diameter of the thoracic duct varied between I and 7 mm. (Table IV). No difference in distribution of size was detected between the groups with and without mediastinal masses.

Valves in the thoracic duct were noted in 292 cases (Fig. 9). In the remaining 98 in which the valves were not visible, good filling was obtained in only 23 cases. The maximum number of valves seen was 13. They were located primarily in the upper and mid third of the duct. The valves appeared to be bicuspid and to vary in size.

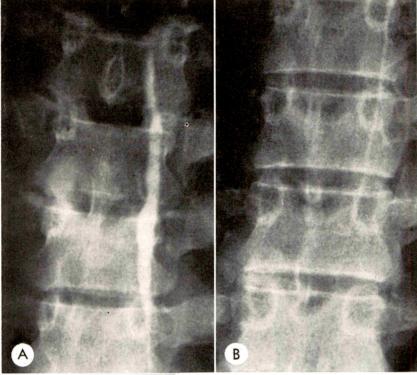




Fig. 5. Thoracic duct. (A) Upper thoracic segment. The thoracic duct lies anterior to the thoracic spine on its left side, immediately adjacent to the descending aorta. Above the left main stem bronchus it parallels the course of the trachea. (B) Mid thoracic portion. The duct in its lower portion moves toward the midline again following the course of the aorta. (C) Caudal segment of the thoracic duct. The lowest portion of the duct overlies the first lumbar vertebra. It is now to the right of the midline. Its most caudal segment is continuous with the cisterna chyli. As it extends cephalad over T-12 and T-11, it begins to move to the left and reaches the left of the midline at the interspace between T-10 and T-11.

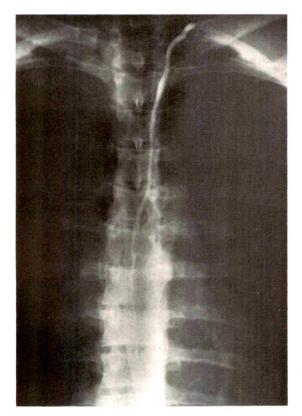


Fig. 6. Thoracic duct. The relationship of the thoracic duct to the spine is variable. In this case it fails to cross to the left of the midline until the level of the 6th thoracic vertebra. Its position with respect to the spine is largely determined by the position of the aorta.

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The maximum observed diameter of a valve was 6 mm.

#### VARIATIONS IN THE THORACIC DUCT

Multiple thoracic channels were observed in 30 cases (Fig. 10). These channels were not a direct continuation of the lumbar trunks but instead arose from the cisterna chyli or from a thoracic duct which then divided. The double thoracic ducts usually terminated in a single duct at the level of the 3rd to 8th thoracic vertebrae. Bilateral superior mediastinal thoracic ducts

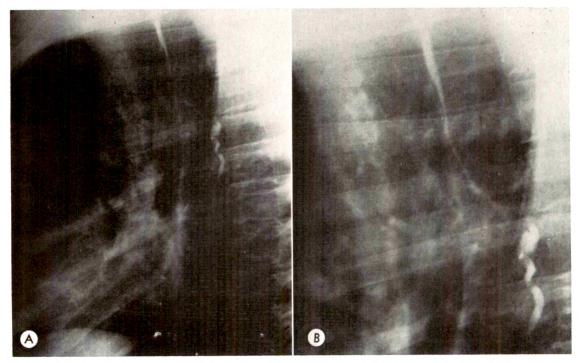


Fig. 7. Course of the thoracic duct. (A) Lateral projection. The close relationship of the duct to the spine and the thoracic aorta is well demonstrated. At the level of the 5th thoracic vertebra, the duct begins to move anteriorly and reaches the level of the posterior surface of the trachea at T-4. (B) Enlargement of upper thoracic duct. The intimate relationship with the arch of the aorta is well demonstrated.

were noted in 6 cases, but the presence of the right thoracic duct was unrelated to double ducts in the lower thoracic portion (Fig. 11, A and B). The cervical segment demonstrated multiple variations including double duct systems, multiple channels, and entry to the right (Fig. 12; and 13). These were observed in about 20 per cent of the cases.

Filling of intercostal lymphatic vessels was observed in the lower portion of the thoracic duct in 2 cases, at the level of the carina in 5 cases, and in the terminal portion of the duct in 2 cases (Fig. 14, A and



Fig. 8. Thoracic duct. Cephalic segment. The upper one-third of the duct resembles an inverted "J." Notice that it becomes three separate channels just prior to its entry into the junction of the internal jugular and the left subclavian veins. A few supraclavicular lymph nodes are filled with contrast agent.

TABLE IV
DIAMETER OF THORACIC DUCT\*

Diameter (mm.)	No. of Patients				
0-1	72				
1-2	66				
2-3	70				
3-4	70 44 64 30				
4-5	64				
5-7	30				

<sup>\*</sup> Because the diameter of a single thoracic duct was variable, the measurement employed is the maximum diameter.

## B). In most of these patients the paravertebral lymph nodes were also opacified.

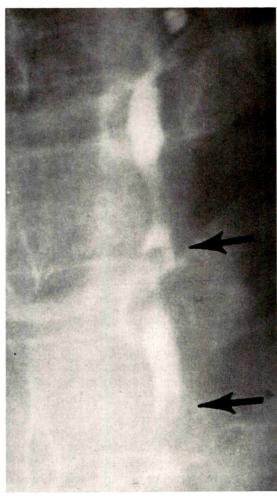


Fig. 9. Valves in the thoracic duct. Valves can usually be visualized in the thoracic duct and vary in number from 2 to 13. They are bicuspid and quite variable in size. The maximum observed diameter of a valve was 6 mm.

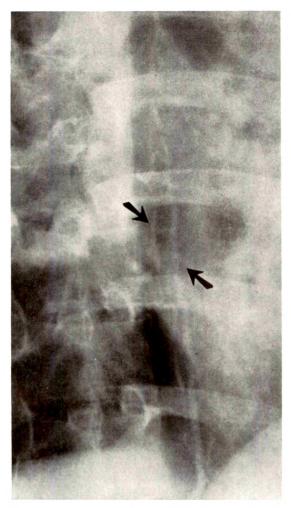


Fig. 10. Double thoracic duct. The thoracic duct is divided at its entry into the thorax into two separate channels, which reunite just below the level of the carina into a single thoracic duct.

#### ABNORMALITIES OF THE THORACIC DUCT

In normal individuals the distance between the lateral tracheal wall and the thoracic duct was 3 to 10 mm. (Fig. 5C; and 6). In the presence of mediastinal masses the thoracic duct was frequently separated from the trachea and produced a tracheal wall-thoracic duct distance greater than 10 mm. (Fig. 15). This was a useful index of the presence of paratracheal lymph nodes which were not visible on the conventional chest roentgenograms.

Kinking of the thoracic duct was observed in 37 cases and was usually related

to a mediastinal mass (Fig. 16, A and B). Tortuosity was seen in 7 cases in association with mediastinal lymph nodes or suggestive evidence of partial obstruction (Table v). Displacement of the duct by a mediastinal mass was observed in 15 cases. Tortuosity of the aorta and kyphoscoliosis were associated with duct displacement. In 1 patient a pneumonectomy with consequent shifting of the mediastinum produced profound displacement of the duct. The major displacements due to mediastinal masses were at the level of the carina or in the left paratracheal region.

#### DISCUSSION

#### THE CISTERNA CHYLI

According to Schdanow the cisterna chyli is absent in 42 per cent of cases<sup>27</sup>—a figure in concord with our own observations. The cisterna chyli was visualized by lymphangiography in 43 of 115 patients studied by Pomerantz *et al.*<sup>23</sup>—a figure significantly lower than ours. Because the cisterna chyli may be empty at various phases of the examination, systematic filming would almost certainly yield a higher incidence of visualization than presently recorded figures.

The location of the cisterna chyli between T-12 and L-2 is consistent with prior observations. The length of the cisterna chyli, said to be 3 to 4 cm. on the basis of anatomic studies, 18,26 is somewhat greater during life, as observed by lymphangiography.

 $\label{eq:Table V} T_{\text{ABLE }V}$  Appearance of the thoracic duct in the presence of mediastinal masses

Abnormality	No. of Patients
Kinking	37
Tortuosity	7
Displacement	15
Dilatation of the cisterna chyli	2
Dilatation of the caudal segment of the duct	2
Delayed emptying of the thoracic duct	ī
Total	82

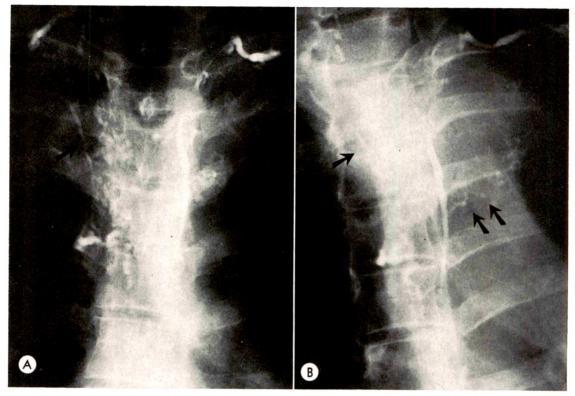


Fig. 11. Bilateral superior mediastinal thoracic duct. (A) Anteroposterior projection. The larger duct is on the left side, but the right duct clearly is carrying a significant amount of oil and there is in addition filling of right superior mediastinal lymph nodes. (B) Oblique projection demonstrates the 2 ducts and the filling of some intercostal lymphatics (double arrow).

#### THE THORACIC DUCT

Congenital variations. Many anatomic variations have been noted in the thoracic duct.14,27 These are related to the origin of the lymphatics from multiple venous buds and to early alterations in fetal development.25 Because there are paired ducts in the embryo, 18,22 it is easy to understand how their persistence may yield a doubleduct system in man. Variations have been described in anatomic,17 pathologic,18 and surgical studies.30 Within recent years lymphangiography has permitted thoracic duct visualization in a high proportion of cases and has contributed to our knowledge of the duct in health and disease. 8,22,23 In some studies the presence of a single thoracic duct throughout its course has been found in little more than one-third of patients:30 the single duct was the variant rather than the double duct. In our own

material, however, duplication of the thoracic duct was not apparent in such a large group of patients nor have other anatomic and lymphangiographic studies supported this finding. Celis and Porter,<sup>7</sup> and Nusbaum *et al.*<sup>22</sup> found a single duct "in most cases." Nevertheless, the fact that 2 ducts may be present at the level of the diaphragm has obvious significance in the surgical treatment of chylothorax.<sup>30</sup>

The variations in the terminal portions of the thoracic duct are also significant not only because this is a common site of trauma but also because major surgical dissections in this area are common. Anatomic studies confirm the presence of multiple channels as shown by lymphangiography and emphasize the relative variability of the venous termination of the duct.<sup>14</sup> In two-thirds of cases the terminus is in the internal jugular vein, and in one-third it



FIG. 12. Cervical segment of the thoracic duct. Multiple channels are visible with tortuosity and localized dilatation. The arrow points to some contrast medium layering in the internal jugular vein. Note the marked separation of the thoracic duct from the lateral wall of the trachea and the superior mediastinal mass extending into the supraclavicular region.

may be in the subclavian, innominate, or external jugular vein.<sup>14</sup>

Size. The size of the normal duct has been estimated at 2 to 8 mm.<sup>22</sup> Because of the wide range of normal variation, size has not been useful as a single determinant of obstruction of the thoracic portion of the duct, although venous hypertension is usually associated with dilatation. In one study of right heart failure, increased size up to 9 mm. in diameter was noted but without a direct relationship between the venous pressure and the degree of dilatation.<sup>31</sup> The lumbar lymphatics were not dilated nor was reflux into intestinal lymph

channels observed. Portal cirrhosis is also accompanied by dilatation of the duct—presumably because of increased lymph production.<sup>29</sup> Even with obstruction to the duct by tumor, the size need not be increased significantly if collateral pathways have taken over,<sup>31</sup> but dilatation of the abdominal portion of the duct and the cisterna chyli have been described with obstruction.<sup>22,23</sup>

Valves. Valves have been noted in less than one-third of patients in one series.<sup>23</sup> In our cases valves were visible in most patients in whom good duct filling was accomplished. Similar observations have been made by Nusbaum et al.22 In conformity with other observers we found the valves primarily located in the upper segment of the duct at the level of the carina and above. Although the valves are usually separated from each other by a distance of 4 to 8 cm., 18 in some cases with II or I2 valves they were much closer together. Lymphangiographic observations of the bicuspid character of the valves are supported by anatomic studies.18

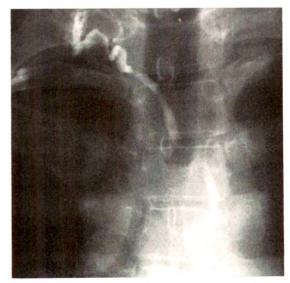


Fig. 13. Cervical segment of the thoracic duct. Right-sided duct. The thoracic duct crosses the midline posterior to the trachea, moves to the right, and enters the junction of the right subclavian and right internal jugular veins. The distance between the left lateral wall of the trachea and the thoracic duct is 9 mm. (within the normal range).

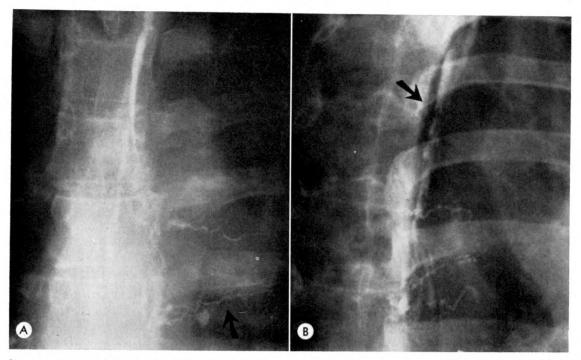


Fig. 14. Intercostal lymphatics. (A) Anteroposterior view. Reflux into the intercostal lymphatics and filling of a small lymph node are visible (arrow). (B) Left posterior projection. Note also the excellent demonstration of valves.

Mediastinal masses. Pomerantz et al.23 found relatively little difference in the appearance of the thoracic duct in patients with intrathoracic disease and those without. Others33 have described total obstruction of the thoracic duct by a mediastinal mass. The thoracic duct may provide a further index of the presence and location of a mass when it is evident on the conventional roentgenograms, or it may demonstrate a mass not previously visible. The tracheal wall-thoracic duct distance is particularly useful and should not exceed 10 mm. in the normal patient. To our knowledge this measurement has not been previously described. Kinking and tortuosity of the duct are very commonly caused by a mediastinal mass although the aortic course must also be appraised in evaluating tortuosity. Displacement of the duct is a further sign, but this may also be related primarily to the position of the aorta.

Obstruction. Although the literature contains descriptions of patients with thoracic duct obstruction, <sup>22,23</sup> the lymphangio-

graphic criteria for the diagnosis are by no means clear cut. Celis et al.,8 in a postmortem roentgen study in man, demonstrated duct obstruction by carcinomatous metastases. The duct was dilated and collateral pathways could be shown. After ligation of the thoracic duct, collaterals develop rapidly in animals.8,19 Other experimental studies in which the duct has been ligated have shown initial dilatation of the duct, increasing prominence of collateral pathways, and development of lymphaticovenous communications.5,21 The lumbar lymphatic chains and nodes became distended and intralymphatic pressure rose initially but gradually returned to normal over a period of weeks.21 Studies in man after ligation have shown that some patients exhibit no evidence of obstruction 3 to 7 months later, but others have partial obstruction as indicated by delayed emptying of the thoracic duct.23 Wallace et al.33 emphasized dilatation of the cisterna chyli and the collateral upper abdominal pathways in a report of a single case of thoracic duct obstruction by a



Fig. 15. Abnormal tracheal wall-thoracic duct distance. Notice the wide separation between the upper segment of the thoracic duct and the lateral wall of the trachea (well beyond the normal of 1 cm.). This was in a patient with Hodgkin's disease of the mediastinum.

"posterior mediastinal mass." Because of the richness of the collateral circulation, it is possible to ligate the thoracic duct in man without significant harmful effects.<sup>23</sup>

The explicit diagnosis of thoracic duct obstruction can be made when there is good visualization of the duct, a sharp cut-off in its course, dilatation proximal to the cut-off, associated tortuosity, visualization of collateral lymphatic and/or lymphaticovenous communications, and delayed emptying. In the absence of a clear demonstration of the site of obstruction or in

partial obstruction, the diagnosis may be more difficult.

Size is helpful but not conclusive because the range of normal variation is wide. Some have considered a diameter larger than 5 mm. to be abnormal.<sup>29</sup> As a single criterion, however, this is inadequate: the normal duct may be equally large.

Collateral channels are usually a helpful index of obstruction<sup>33</sup> but must be viewed with caution. Filling of retroperitoneal pathways and lymphaticovenous communications is valuable evidence, but intercostal lymphatics may at times fill in the absence of thoracic duct obstruction.

Delayed emptying of the thoracic duct is probably a reliable sign of obstruction and was seen in I patient in our series with obstruction. It has also been observed in patients with right heart failure.

Mediastinal lymph node opacification has also been considered evidence of lymphatic obstruction.<sup>23,31</sup> Although this may be significant, in particular if right paratracheal lymph nodes are filled, mediastinal lymph node opacification may also be observed as a normal phenomenon.

Kinking, tortuosity, and displacement of the thoracic duct are usually caused by a mediastinal mass and may be associated with obstruction.

#### THORACIC DUCT LACERATION

There are now considerable data on lacerations of the thoracic duct and their association with chylothorax9,11,15,22,24 and chylous ascites.10 Trauma, operative injury,9,22 premature puncture during translumbar aortography,11,15,28 spontaneous rupture due to coughing or retching, and rupture consequent to neoplastic obstruction and invasion18,31 may be causes of a leak of chyle and the development of chylothorax. Because conservative management may be unsatisfactory, surgical therapy may be necessary. Lymphangiography is immensely valuable in defining the site of laceration and the direction of the flow of the extravasated lymph. After preoperative identification of the leakage site, excellent surgical repair has been obtained.15

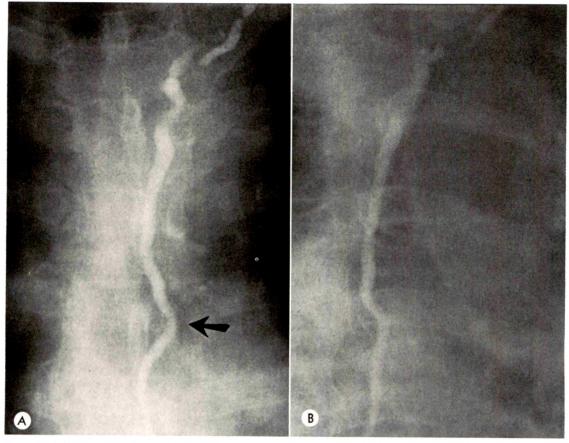


Fig. 16. Kinking of the thoracic duct. (A) Anteroposterior projection. The arrow points to localized kinking near the left main-stem bronchus. This finding was almost invariably associated with the presence of a mediastinal mass. Note also the separation of the thoracic duct from the lateral wall of the trachea. (B) Oblique projection. Further evidence of the kinking due to enlarged lymph nodes is apparent.

#### SUMMARY

The appearance of the thoracic duct was analyzed in 390 sequential lymphangiograms.

The classic bulbous dilatation of the cisterna chyli was visualized in 53 per cent of cases. It was located at the T-12 to L-2 levels and was usually less than 5 cm. in length.

The thoracic duct varied in size from I to 7 mm. Valves were visible in 84 per cent of cases (usually in the upper third of the duct). Double thoracic ducts, bilateral superior mediastinal ducts, and multiple variations in the cervical segment of the duct were observed. Intercostal lymphatic vessels were occasionally filled in normal studies. In the presence of mediastinal

masses, the distance between the lateral tracheal wall and the thoracic duct measured greater than the normal of 10 mm. Kinking, tortuosity, and displacement of the duct were also apparent.

Thoracic duct obstruction may be diagnosed by a sharp cut-off in its course, dilatation, tortuosity, visualization of collateral channels, and delayed emptying. If the site of obstruction is not clearly defined or if the occlusion is partial, delayed emptying and collateral visualization are the most helpful criteria. Opacification of mediastinal lymph nodes may at times occur normally.

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## THE RADIOGRAPHIC MANIFESTATIONS OF AMYLOIDOSIS\*

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AMYLOID is an abnormal protein, probably a glycoprotein, to which ably a glycoprotein, to which a mucopolysaccharide may be attached. It is deposited within parenchymatous and mesenchymatous tissues and around blood vessels where it does not evoke an inflammatory response but compresses and replaces normal tissue and interferes with cellular and organ physiology. Current investigations indicate that amyloid is not an amorphous hyaline substance but consists of a highly distinctive fibrillary structure as seen by electron microscopy. This structure is similar in all forms of amyloid: human or animal, primary or secondary, regardless of location.

The pathogenesis of amyloidosis is unresolved. Unquestionably there is some basic relationship between amyloid and abnormalities in immune mechanisms, and many conditions known to predispose to amyloidosis are accompanied by plasmacytosis and hypergammaglobulinemia. This is not consistently true, however, and the disease may occur with agammaglobulinemia. It is no longer held that amyloid is an antigen-antibody precipitate or an altered or fragmented immunoglobulin formed by the plasma cell. Instead, present concepts suggest that the same factors resulting in stimulation of the plasma cell and in hypergammaglobulinemia, as well as other undefined stimuli, evoke proliferation of protein-synthesizing reticuloendothelial cells.2,6 This may not even be exclusive to the reticuloendothelial system since epithelial cells of the thyroid and pancreas, and possibly fibroblasts of the skin, may also elaborate amyloid.

Amyloidosis is unquestionably of greater importance and is more frequent than

usually appreciated. It is difficult to determine its true incidence since some studies refer only to clinically evident disease, while others relate to microscopic detection of small deposits of amyloid by scrupulous observers utilizing special stains and even polarizing or electron microscopes.

Amyloidosis occurs in between 0.22 to 0.5 per cent of routine postmortem examinations, in 10 to 15 per cent of patients with multiple myeloma, in probably 20 to 25 per cent of patients with rheumatoid arthritis, 23.6 per cent of paraplegics, 26 to 40 per cent of individuals with familial Mediterranean fever, and in up to 50 per cent of victims of chronic tuberculosis and leprosy.5,7,10 Cohen and Wills7 found deposits of amyloid in 16 per cent of 100 consecutive postmortem examinations of patients whose average age was 80 years (with a range of 56 to 96 years) and this closely corroborates similar studies and confirms an increasing incidence of amyloidosis in the aged.

#### CLINICAL AND RADIOGRAPHIC FINDINGS

The clinical manifestations of amyloidosis are diverse and include intractable heart failure, conduction irregularities, digitalis sensitivity, nephrosis, uremia, malabsorption and malnutrition, purpura, polyneuritis and the carpal tunnel syndrome.

The radiographic features are also varied and none are absolutely pathognomonic, but when considered in their totality they can suggest or corroborate the diagnosis of primary or secondary amyloidosis.

#### CLASSIFICATION

Amyloidosis may appear to arise primarily either sporadically or as part of a

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Table I

DISORDERS COMPLICATED BY AMYLOIDOSIS

Chronic Inflammatory Diseases

Tuberculosis

Leprosy

Syphilis

Osteomyelitis

Bronchiectasis

Pyelonephritis

Reiter's disease

Whipple's disease

Regional enteritis

Ulcerative colitis

Connective Tissue Disorders

Rheumatoid arthritis

Other collagen vascular diseases

Paraplegia

Post-traumatic

Other

Metabolic disease

Diabetes

Plasma Cell Dyscrasias and Neoplasias

Multiple myeloma

Waldenström's macroglobulinemia

Heavy Chain disease

Other Neoplasms

Hodgkin's disease

Renal cell carcinoma

Medullary thyroid carcinoma

Others

heredofamilial complex. Secondary amyloidosis occurs in a wide variety of inflammatory and even neoplastic diseases, <sup>16</sup> and with rheumatoid arthritis and collagen disorders (Table 1). A form clinically resembling primary amyloidosis occurs in association with multiple myeloma, Waldenström's macroglobulinemia, Heavy Chain disease and with plasma cell dyscrasias. Amyloid also is found as a manifestation of aging. The deposits may be generalized or localized, diffuse or tumefactive. All classifications attempt to correlate these many variations (Table II).

Amyloidosis has also been classified as "typical" when parenchymal organs are involved and "atypical" when the manifestations are within organs other than the kidney, liver, spleen or adrenals. Recent studies indicate that there are no categoric differences in organ involvement in primary, secondary, in myeloma-associated or

plasma cell dyscratic amyloidosis.<sup>3</sup> Despite this, some slight clinical differentiation may accrue through the use of this distinction. Virtually all cases of secondary amyloidosis exhibit initial infiltration of a parenchymal organ such as the kidney, liver, spleen or an endocrine gland, while those with primary or myeloma-associated amyloidosis more frequently first present with mesenchymal involvement.<sup>5</sup>

#### PARENCHYMAL ORGANS

Regardless of classification, renal disease is eventually a major component of the illness. Radiographically the kidney may appear enlarged, normal, or decreased in size. Enlargement is probably not as frequent as formerly believed but is most suggestive of amyloidosis when it occurs in the presence of renal failure or the nephrotic syndrome. Brandt, Cathcart and Cohen<sup>3</sup> observed one patient whose kidney diminished in size from 15 to 11 cm. in 6 months, apparently due to amyloidotic involvement of the renal microcirculation with resultant ischemia and fibrosis. Case I (Table IV) also showed vascular narrowing and even occlusion resulting in ischemic obsolescence of glomerular tufts.

#### TABLE II

#### ANOTHER CLINICAL CLASSIFICATION OF AMYLOIDOSIS

 Primary Amyloidosis (with no apparent predisposing cause)

Sporadic with atypical distribution

Sporadic with typical distribution

Tumor-forming amyloid 2. Heredofamilial Amyloidoses

Familial amyloid polyneuropathy (various

Amyloidosis with familial Mediterranean fever

Familial amyloid cardiopathy
Familial amyloid nephropathy

Familial cutaneous amyloid

Familial medullary thyroid carcinoma with amyloid

- Secondary Amyloidosis (with associated inflammatory, neoplastic and other diseases)
- 4. Amyloidosis Accompanying Multiple Myeloma, Waldenström's Macroglobulinemia, Heavy Chain disease and Plasmacytosis
- 5. Senile Cardiac Amyloidosis

The liver is almost invariably involved microscopically in all forms of amyloidosis, but hepatomegaly, unrelated to congestive failure, is found in only 64 per cent of cases. Weights over 4,000 grams and even to 6,000 and 9,000 grams are reported. 4.6 Liver enlargement can occur with few signs and symptoms of liver insufficiency; ascites is rare and late.

Pathologic involvement of the spleen is also extremely frequent, but clinically recognizable enlargement is limited to between 20 to 30 per cent of cases (Fig. 1; Case VII).<sup>3,4</sup>

The pancreas, adrenal, thyroid, parathyroid, pituitary and salivary glands are affected to varying degrees and Addison's disease and Sjögren's syndrome have been attributable to amyloidosis. Amyloidotic infiltration of the thyroid can result in massive goiter and should be included in the differential diagnosis of radioscanning abnormalities of that gland.<sup>19</sup>

#### CARDIOPULMONARY SYSTEM

Statistically the heart is more often affected in primary or in myeloma-related amyloidosis than in the secondary form, but there is a distinctive clinical variety—so-called senile cardiac amyloidosis—in which the heart is the principal and generally the only organ involved. Senile cardiac amyloidosis is the commonest form of amyloidosis and has been reported in 10 per

## TABLE III COMPLICATIONS OF AMYLOIDOSIS

Gastrointestinal Bleeding From
Esophageal varices
Esophageal ulcer
Gastric erosion
Gastric and duodenal ulcer
Small and large bowel hemorrhage
Perforation of Esophagus
Perforation of Small Intestine
Rupture of Spleen
Intracapsular Hematoma of Liver
Pancreatitis
Pathologic Fracture of Femur
Avascular Necrosis of Femoral Head



Fig. 1. Secondary amyloidosis occurs in 20 to 25 per cent of patients with rheumatoid arthritis but in only 4 per cent of children with Still's disease. Case vII (Table IV) is a 10 year old boy with juvenile rheumatoid arthritis since age 3½ years with microscopically proven amyloid and splenomegaly (arrows).

cent of patients over 80 years of age and in 50 per cent of those over 90 years and may be the only apparent cause of cardiac failure. An autoimmune phenomenon has been hypothesized as the cause of amyloidosis in the aged.

Within the heart, amyloid characteristically occurs as endocardial atrial nodules, but it may also surround, compress and replace myocardial fibers and involve vessel walls, valves, pericardium and aorta.

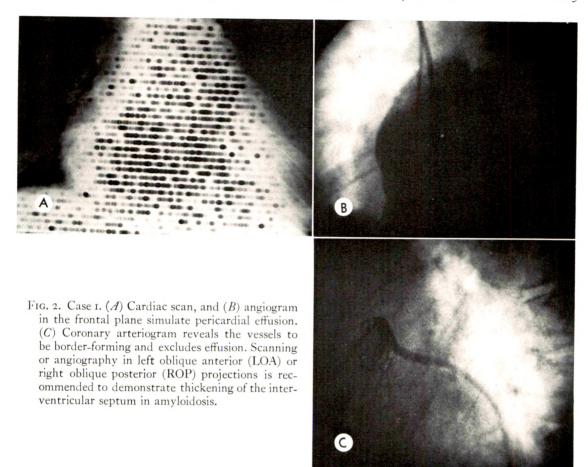
The heart may be grossly increased in size. The largest amyloid heart weighed 1,090 grams or 5 times normal compared with the patient's marantic total bodily weight of 41 kg.<sup>11</sup> The heart, however, may be normal in size, or if thoroughly infiltrated, may be small.

Fluoroscopy is frequently disappointing

## TABLE IV

# SUMMARY OF FINDINGS IN 9 CASES

	675 grams, diffuse severe myocardial, amyloid				tumor" eeter, ic evil myloid							Amyloid Senile Cardiac Ureter Amyloidosis
Case VIII F.McD. 090756 SJ 73 M (Patient alive)		amyloid "tumor" of right ureter, microscopic evi- dence of amyloid in kidney								Tumoral Amyloid of Right Ureter		
Case VII M.L. 213513 CGH 10 M (Patient alive)				splenomegaly, positive biopsy for amyloid								Secondary Amyloid with Rheumaloid Arthritis From Age of
S.N. 217668 CGH (Patient alive)	cardiomegaly	pneumonectomy for tuberculosis			nephrotic syndrome, positive needle biopsy for amyloid						smooth stiff aperistaltic esophagus	Clinically Secondary Amyloidosis with Rheumatoid Arthritis, Proteinuria and Neprotic Syndrome Gastrointestinal Hemorrhage, Site Undetermined
Case V G.D. 407309 SJ 65 F (Patient dead but no autopsy)	cardiomegaly		hepatomegaly							pseudoscleroderma	macroglossia, thickened bowel, atonic esophagus aspiration of barum, positive biopsy	Plasmacytosis of Bone Marrow, Oseous Lesions, Abnormal Electro- phoresis with 30.85 per cent Gamma Globulin
Case IV W.J.A. 60-41 PMH 42 M	420 grams, vascular, myocardial	vascular	1,460 grams, vascular	210 grams, subintimal	R 200 gm.; L 160 gm.; vascular and within glomerular tufts	vascular					vascular with areas of mucosal deposition	Primary Amyloi- dosis, Cardiac fail- ure, Polyneuritis, Sprue Syndrome
Case III A.B. 64-61 CGH 44 F	250 grams, myo- cardial, endocar- dial, valvular	vascular	r,500 grams, vascular	200 grams, vascular	R 50 gm.; L 60 gm.; arteries and arterioles thickened and some occluded		vessels and sup- porting tissue	vascular	adventitial vessels	muscles and sub- cutaneous fat	vascular and mus- cular amyloid with thickened duo- denal and jejunal walls	Multiple Myeloma with Systemic Amyloidosis, Mye- loma of Kidney, Uremia
Case II E.F. 67-A-225 SJ 67 M	375 grams, perivascular, subendo-thelial, myocardial	vascular walls in- cluding tracheo- bronchial vessels	1,750 grams, vascular and sinusoidal	350 grams, vascular and sinusoidal	R 155 gm.; L 150 gm.; vascular and slight parenchymal	vascular and in- terstitial	adrenal and peri- adrenal vessels		wall	pseudoscleroderma vessel walls and muscle bundles	mucosa of esophagus ulcerated, thick wall throughout bowel	Primary Amyloi- dosis with Involve- ment of Blood Vessels, Nerves, Heart, Lung, Liver, Spleen and
Case I L.S. 69-A-172 SJ 64 F	550 grams, myo- cardial, vascular, tricuspid valve	vascular walls and alveolar septa	1,450 grams, vascular	180 grams, peri- vascular	R 110 gm.; L 110 gm., vascular with ischemic changes of glomerular tufts	vascular and par- enchymal	vascular	vascular	adventitial vessels	perivascular	vascular walls of submucosa, mus- cularis and serosa	Primary Amyloidosis with Cardiac and Renal Failure and Diffuse Vascular Involvement of Lung, Gastrointestinal Tract, Endocrine Glands, Liszer and Schoen
	Heart	Lungs	Liver	Spleen	Kidneys	Pancreas	Adrenals	Thyroid and parathyroid	Aorta	Subcutaneous	Gastrointestinal	Diagnosis



in evaluation of infiltrative disease of the myocardium, but occasionally typically muted pulsations are noted.

The disease may simulate pericardial effusion clinically, on routine roentgenograms and by frontal angiography and radioscanning (Case 1; Fig. 2, A-C); however, differentiation is possible by appropriate angiographic and scanning projections which demonstrate thickening of the interventricular septum. Similarly, visualization of the coronary arteries at the border of the cardiac silhouette will distinguish thickened myocardium from effusion.

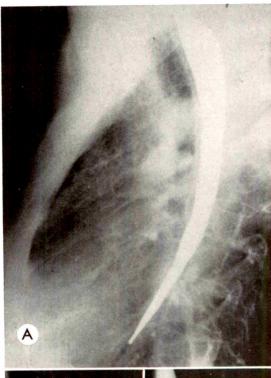
Cardiac amyloid is frequently associated with perivascular and interstitial pulmonary deposits which are usually indistinguishable from or obscured by associated pulmonary congestion. More exuberant infiltrations, however, resemble other forms of disseminated interstitial pulmonary disease.

Subepithelial collections of amyloid also occur within the tracheobronchial tree where they elevate the mucosa, producing ridges, plaques or nodules which become visible bronchographically when they project into the trachea or large bronchi or when they cause fusiform areas of stenosis within the smaller airways.<sup>15</sup>

#### GASTROINTESTINAL TRACT

The most dramatic radiographic manifestations of amyloidosis occur within the gastrointestinal tract which may be affected from gingiva to rectum. Indeed these extremes of localization, especially the latter, are highly reliable sites for random biopsy diagnosis of amyloidosis.

Macroglossia is often present but even



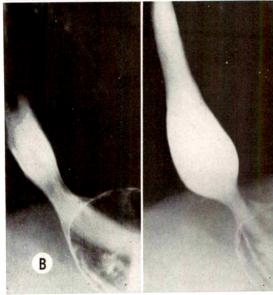


Fig. 3. No categoric differences in organ involvement occur in primary vs. secondary amyloidosis. The esophagus is smooth, stiffened and aperistaltic (A) in Case vi with rheumatoid arthritis, and (B) in Case ii with primary amyloidosis.

without gross enlargement, infiltrations may so stiffen the tongue as to interfere with swallowing. Involvement of the esoph-

agus results in a smooth, tubelike, aperistaltic organ resembling scleroderma and dermatomyositis (Fig. 3,  $\mathcal{A}$  and  $\mathcal{B}$ ; Cases II and vI). Unlike the former, but similar to the latter, amyloid affects striated as well as smooth muscle and can result in pharyngeal dysphagia and nasal regurgitation (Fig. 4,  $\mathcal{A}$  and  $\mathcal{B}$ ; Cases III and v). Esophageal ulceration and erosion are not uncommon.

Nodular submucosal masses of amyloid have been described within the stomach where they resemble polypoid carcinoma, but usually there is smooth stiffening and shortening resembling infiltrating neoplasm (Fig. 5). Upper gastrointestinal hemorrhage is frequent secondary to gastric and duodenal erosions and ulcerations at sites of amyloid infiltrations.

A striking finding on routine roentgenograms of the abdomen is delineation of marked thickening of the wall of the stomach and intestine (Fig. 6,  $\mathcal{A}$  and  $\mathcal{B}$ ). The loops of intestine do not float centrally as in ascites.

Within the small intestine the spectrum of roentgen change ranges from virtually undetectable stiffening of the bowel wall to marked thickening, rigidity and atonicity. Gross increase in width of the valvulae conniventes differentiates amyloidosis from scleroderma with which it may be confused. Dilatation does occasionally occur and there may be marked delay in passage of barium which may remain within the small intestine for days simulating mechanical obstruction to the unwary (Fig. 7, A–C).

The changes within the large intestine are less readily discernible but there may be stiffness, smoothness, loss of normal haustrations and occasionally stricture-like narrowing and even polypoid changes. Amyloidosis may mimic and coexist with ulcerative colitis and regional enteritis.

Gastrointestinal complications are unexpectedly common and include perforation of the esophagus and small bowel, bleeding from esophageal varices, gastric and duodenal ulceration, diffuse small and

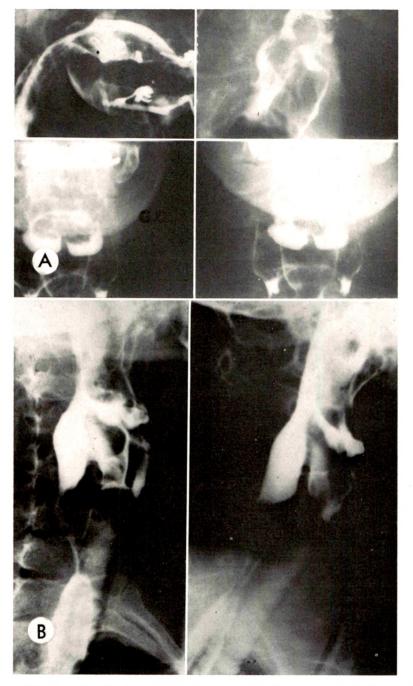


Fig. 4. The tongue is infiltrated and enlarged (A) in Case v, and both Case v and (B) Case III show abnormal deglutition due to amyloid infiltrating the tongue and striated muscles of the pharynx.

large bowel hemorrhage, diarrhea, obstruction, malabsorption, protein-losing enteropathy, intracapsular hepatic hematoma and pancreatitis.<sup>1,3,6</sup>

#### BONES AND JOINTS

The carpal tunnel syndrome is a common complication of all forms of amyloidosis. Amyloidotic arthritis results from



Fig. 5. Infiltration of the wall of the stomach simulates carcinoma in Case II. A duodenal ulcer is present and gastrointestinal hemorrhage is a common complication of amyloidosis.

extensive amyloid infiltration of the synovium. It may resemble rheumatoid arthritis clinically but radiographically there

is no evidence of associated articular change.<sup>12</sup> Subluxations can occur due to the profound synovial thickening.

APRIL, 1971

Microscopic and gross deposits of amyloid can be found within the bone marrow in multiple myeloma. Weinfeld and associates<sup>20</sup> have indicated that this can lead to generalized demineralization and vertebral collapse. Less commonly, areas of bone destruction or even avascular necrosis are secondary to deposition of amyloid within the nutrient vessels.

More typically, bone destruction results from marked amyloidotic synovial proliferation which invades bone in the region of a joint and is radiographically analogous to the bony erosion seen in pigmented villonodular synovitis. Generally, multiple and larger joints are involved than in the latter (Fig. 8). The destruction may be so extensive as to cause pathologic fracture.

#### SUBCUTANEOUS TISSUES

A wide variety of amyloid lesions involves

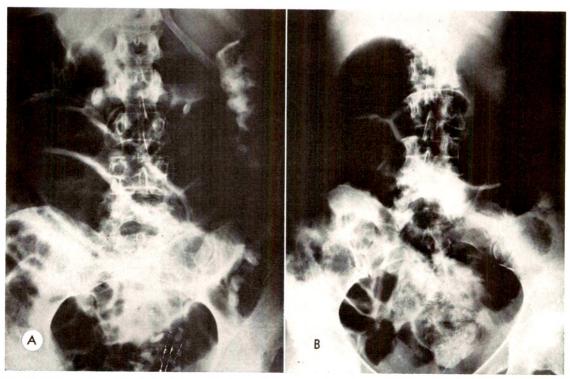
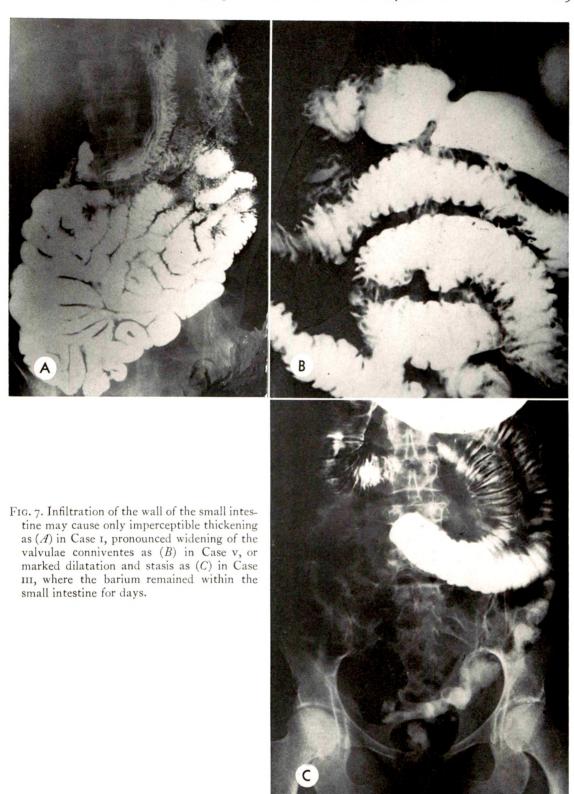


Fig. 6. Thickening of the wall of the stomach and of the intestines is a striking manifestation of amyloidotic infiltration as in (A) Case III and (B) Case v. There are no signs of ascites. Constipation is common.



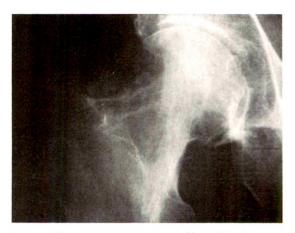


Fig. 8. The most common type of bone involvement occurs secondary to amyloidotic thickening of the synovium which may cause subluxation or which may invade bone in a manner analogous to pigmented villonodular synovitis. (Courtesy of Dr. Benjamin Felson, Cincinnati, Ohio.)

the skin and mucous membranes. Generally these are purpuric spots and small papules,<sup>6</sup> but some cause waxy thickening of the skin simulating scleroderma and the terms "pseudoscleroderma" and "scleroderma amyloidosum" have been used for this clinical variant<sup>13</sup> (Fig. 9, A and B; Cases III and v). This erroneous impression can be enhanced by radiographic findings of cardiac and gastrointestinal involvement which also mimic scleroderma.

Fine stippled calcifications within the subcutaneous fat of the trunk (Fig. 10), thoracic cage, flanks, abdominal wall and within the labia majora have been described in a case of amyloidosis associated with Waldenström's macroglobulinemia.<sup>8</sup>

#### TUMORAL AMYLOID

Tumor-forming amyloid occurs without apparent systemic disease, especially within the upper respiratory tract and urinary bladder, but also within the eye, pharynx, larynx, lower respiratory tract, ureter and urethra. Plasma cells and lymphocytes are not infrequently found in conjunction with these nodules and it is of note that these are the same organs affected by extramedullary plasmacytomas.

Single or multiple asymptomatic pul-

monary nodules composed of amyloid vary in size from millimeters to centimeters. Their appearance is noncharacteristic but calcification is very frequently present and many lesions undergo cartilaginous metaplasia and actual ossification. <sup>18,20</sup> Cavitation has also been noted.

Similar tumors may occur within one or both ureters<sup>9</sup> (Fig. 11).

The concept of isolated tumoral amyloidosis, like that of isolated senile cardiac amyloidosis, may be an oversimplification since other foci are occasionally found, as in Case VIII where microscopic evidence of amyloid was also found in the resected kid-





Fig. 9. Amyloid infiltrations within the subcutaneous tissues cause thickening and obliteration of the usual skin folds simulating scleroderma. (A) Case III, and (B) Case v had multiple myeloma and a lytic lesion is present in the base of the first metacarpal bone in the former (arrow).

ney. In one report of 29 cases of cardiac amyloid, 11 subsequently showed other sites of involvement.<sup>6</sup>

#### SUMMARY

Amyloidosis is a multiple system disease which may occur primarily, either sporadically or as part of a heredofamilial disease, or secondarily in association with a wide variety of inflammatory and neo-



Fig. 10. Foci of fine stippled calcification within a matrix of amyloid deposited in the subcutaneous tissues of the trunk of a woman with Waldenström's macroglobulinemia. These are seen best along the rib cage, bilaterally, as well as within the flanks and labia majora. The calcific deposits are irregular and not arranged in sheets as is usually the case in dermatomyositis.8 (Reproduced with permission of the New England Journal of Medicine.)



Fig. 11. Tumor-forming amyloid invading the wall of the right ureter in Case VIII resulted in ureteropyelocaliectasis. Microscopic evidence of amyloid was found in the resected kidney without evidence of amyloid elsewhere.

plastic disorders, including Hodgkin's disease and renal cell carcinoma. At present, aging, rheumatoid arthritis, paraplegia, multiple myeloma and plasma cell dyscrasias appear to be the most frequent concomitants of amyloidosis.

Radiographic manifestations of amyloid may be seen in the heart, lungs, kidneys, spleen, liver, gastrointestinal tract, subcutaneous tissues, bones and joints. Although the roentgen findings are not pathognomonic, they can be suggestive or corroborative, particularly in the presence of an associated secondary disease. Conversely, roentgen findings consistent with amyloidosis should promote search for an accompanying disorder.

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## SEATBELT INJURIES OF THE SPINE AND ABDOMEN

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THE automobile seatbelt has, without question, saved many lives and prevented many serious head and facial injuries since its gradual introduction into the American automobile in the past 15 years. Presently, every new car sold is required to be equipped with combination lap-and-diagonal belts. The use of seatbelts is now widespread, despite continuing neglect by many drivers and passengers who risk injury and death without the belt.

The life-saving seatbelt may rarely inflict serious injury upon the spine and intraabdominal contents. Scattered reports describe a wide variety of injuries to virtually all abdominal viscera, but perforation of the small bowel and laceration of the small bowel mesentery is especially common. It is now recognized that the seatbelt can produce a predictable variety of injuries to the spine, notably a horizontal fracture of a vertebra with tearing apart of the posterior elements.

This report will review the literature of seatbelt injuries, and describe 10 additional cases collected by the author, with special emphasis on the roentgenographic findings.

## REVIEW OF THE LITERATURE

In 1962, Garrett and Braunstein<sup>9</sup> investigated a large series of accident records to see if a "seat-belt syndrome" (i.e., injury directly attributable to the seat-belt) did exist. They analyzed the records of 3,325 occupants wearing seatbelts in 2,778 automobiles involved in collisions. A total of 150 injuries to the lower torso were found; 47 were sprains in the lumbar region or contusions over the bony protuberances of the hips. There were only 26 serious injuries: 7 pelvic fractures, 7 intraabdominal injuries, and 12 lumbar spine injuries (none illustrated). Two of the 7 cases of intraabdominal injury were documented at operation; I patient had rupture of the duodenum and pancreas; and another was found to have bladder and renal contusions. Only 3 patients were found to have abdominal bruises to indicate a severe restraining action of the belt. The majority of these injuries were thought to be caused by "the severe and unusual nature of most of these accidents," and not by the seatbelt itself. The authors concluded that the seatbelt presents no hazard to occupants, except in unusual and isolated instances.

However, there is now a significant number of published reports of seatbelt injury to the spine and abdomen. There have been at least 20 original articles on seatbelt trauma published in the literature between January 1967 and July 1969.

#### VERTEBRAL INJURIES

At least 40 cases of vertebral injury due to seatbelts are now described in the literature. A horizontal, "fulcrum fracture" of a vertebral body was first reported in 1965 by Howland et al.12; other reports of an almost identical vertebral fracture were soon to follow. 1,3,8,10,22 This fracture is caused by acute, severe flexion over the resisting lap belt. If the ligamentous structures remain intact, the fracture extends through the spinous process and usually through the pedicles and into the posterior aspect of the vertebral body. The transverse processes may also be horizontally split apart. The interspinous ligament may be torn, rather than the spinous process.

Other injuries of the lumbar spine have also been reported, including compression fractures, fracture-dislocations, and isolated fractures of the posterior arch. 13,23,24

The most comprehensive series of seatbelt injuries of the spine has been collected by Smith and Kaufer.<sup>21</sup> They report a series of 24 lumbar spine injuries sustained by accident victims who were wearing a lap seatbelt. Four of these were simple lumbar

compression fractures. The remaining 20 cases showed "an unusual and consistent pattern of injury characterized by separation of the posterior elements without the usually expected decrease in the height of the anterior portion of the vertebral body." Five of these 20 cases were horizontal Chance fractures of a lumbar vertebra. (In 1948, G. Q. Chance4 described 3 patients with unusual flexion fractures of the lumbar spine, consisting of a horizontal splitting of the vertebral body and posterior arch. and separation of the latter. The type of injury was not mentioned. This unique description was lost until Smith and Kaufer<sup>21</sup> recognized the similarity of several of their seatbelt fractures—and first coined the term "Chance fracture" of a vertebra due to seatbelt injury.)

The remaining 15 cases of Smith and Kaufer<sup>21</sup> showed a variety of forms of disruption of the posterior elements; rupture of the interspinous ligament and gross separation of the spinous processes was a constant finding. Many had separation of the facet joints, or a fracture of the superior articular process. Two of the 15 had complete dislocation with anterior displacement of the superior vertebra (both with paraplegia), and 1 had a severe rotational fracture (with paraplegia).

#### ABDOMINAL INJURIES

At least 68 cases of seatbelt trauma to the abdominal contents have been recorded in the literature. The majority of cases involve the small bowel and associated trauma of the small bowel mesentery.

MacLeod and Nicholson<sup>15</sup> reviewed 38 reported cases of seatbelt trauma to the abdomen, and added 3 of their own. Of 31 in which a lap-type seatbelt was implicated, there was a tear of the small bowel and/or its mesentery in 26. Some patients had simple lacerations of the mesentery or bowel; others had extensive trauma in multiple areas of the gastrointestinal tract and severe injury of the mesentery and omentum. In addition to the 26 small bowel perforations there were 3 perforations of the

duodenum and I primarily involving the colon. There were 2 abdominal wall hernias, and other reports of laceration of a solid viscus: kidney (3), liver (2), spleen (2), liver and spleen (1), and pregnant uterus (1). Injuries to the liver and kidney were primarily seen in 5 patients in a series who were wearing a diagonal belt only.

In addition to the comprehensive report of MacLeod and Nicholson, there have been 27 additional cases of seatbelt trauma to the abdomen reported in the literature. McRoberts recorded I case of hemorphagic infarction of the entire small bowel. Shamblin reported I case of jejunal perforation, and another case of complete transsection of the stomach just proximal to the pylorus. Campbell and Austin described I case of laceration and devitalization of large and small bowel, laceration of the inferior vena cava, and delayed dissection of the abdominal aorta. There was an associated compression fracture of L I.

Doersch and Dozier<sup>6</sup> reported 3 cases with mesenteric laceration and infarction, with perforation of either small bowel or cecum. DiFiore and Gin<sup>5</sup> describe 8 major injuries from seatbelt trauma to the abdomen: ruptured liver (3), ruptured spleen (1), perforation of the ileum (2), lacerated mesentery of the ileum (1), and perforation of the jejunum and sigmoid colon (1). Haddad and Zickel<sup>10</sup> reported 1 case of Chance fracture of L 3 associated with jejunal perforation. Backwinkel<sup>1</sup> described a patient with a Chance fracture of L 3 and perforation of the jejunum and "sleeve stripping" of the sigmoid colon; and a second patient with laceration of the mesentery and small bowel. Smith and Kaufer<sup>21</sup> recorded 3 cases of intraabdominal injury in their series of 24 spine fractures; I with complete transection of the jejunum and tears of the colon, I with rupture of the ileum discovered 14 days postinjury, and another with rupture of the liver, spleen, uterus, diaphragm, and mesentery.

There have been reports of injuries with the diagonal seatbelt. Slatis<sup>20</sup> reported 3 patients with abdominal injury with diagonal belts, 2 with "rupture of the mesentery" and a third with rupture of the liver. Hamilton<sup>11</sup> reported 3 patients wearing combination lap-and-diagonal belts with perforation of the duodenum or jejunum. Two of these 3 patients also had fractures of the upper portion of the spine.

#### MATERIAL

Ten cases of seatbelt injury have been collected in the past 4 year period, and are presented in Table 1. Two patients (Cases 4 and 7) were seen at the Indiana University Medical Center Hospitals, Indianapolis, Indiana. Case 1 was seen at the 4500 Hospital, Langley Air Force Base, Virginia. The 7 remaining patients have been seen and treated at Reid Memorial Hospital, Richmond, Indiana.

All 10 patients were wearing the common lap seatbelt at the time of their accident. Each patient had a seatbelt contusion of some degree on the anterior abdominal wall, directly underlying the belt. The specific

details of the accidents are not known in all cases; although most were high-speed collisions, several accidents involved automobiles moving at moderate speed (20–30 m.p.h.). The majority of patients were passengers in the right front seat; none were back seat passengers.

Seven patients of this series were discovered to have a horizontal Chance fracture of a lumbar vertebra with marked disruption of the posterior elements. Three of these 7 patients had intraabdominal trauma, 2 with perforations of the small bowel and another with superficial lacerations of the serosa of the small bowel and mesentery. Three other patients had less serious injury: 1 patient had a compression fracture of D 12 and slight separation of the spinous processes of D 12 and L I, indicating a tearing of the interspinous ligament. Two patients had fractures of the ilium, directly underlying the seatbelt.

All 10 patients recovered without serious disability, although several with lumbar

TABLE I
SUMMARY OF CASES

Case No.	Age	Sex	Vertebral Injury	Abdominal Injury	Other Injury	Treatment	Result
I	27	F	Chance fracture L 3	Two perforations of jejunum; super- ficial laceration of cecum	Severe tearing of abdominal wall tissues	Bowel perforation closed; hyperextension body cast	Recovery—residual back pain
2	20	M	Chance fracture L 3	None	Severe contusion of face; fracture of nasal bone, frontal sinus, and both maxilla	Three facial operations; lumbosacral corset	Recovery—resid ual back pain
3	20	F	Chance fracture L 1; slight compression L 2.	None	Contusion of right orbit	Jewett brace	Slow recovery
4	18	F	Chance fracture L 2	Serosal tears of small bowel	Severe facial lacerations	Laparotomy; exploration of spine with fusion; body cast	Slow recovery
5	20	M	Chance fracture D 12; fracture L 1 body and transverse process	None	Cerebral concussion; facial lacerations	Bedrest; back brace	Recovery
6	19	M	Chance fracture L 1	None	Unconscious; cerebral concussion; facial and hand lacerations; fracture of right clavicle	Bedrest; back brace	Recovery
7	17	M	Chance fracture L 1	Small bowel per- foration	None	Small bowel resection; lateral spine fusion; body cast	Slow recovery
8	20	M	Compression fracture D 12; slight separation spinous processes	None	Scalp laceration	Bedrest	Recovery
9	2 I	M	Slight compression fracture L 4; posterior elements intact	None	Fracture of right iliac crest	Not hospitalized	Recovery
10	72	F	None	None	Fracture of right ilium; bladder contusion	Bedrest	Recovery

spine fractures had continuing back pain several years after their injury. There were no serious neurologic problems. The majority of patients had facial and extremity lacerations and contusions; I patient had severe, central facial fractures requiring 3 plastic surgical procedures. Two patients (Cases 5 and 6) were driver and right-front passenger in the same automobile.

#### REPORT OF SELECTED CASES

Case 1. This 27 year old female was a passenger in the right front seat when her husband went to sleep at the wheel, ran off the road, and hit a large concrete sign. She received a severe contusion of the anterior abdominal wall tissures directly underlying the seatbelt. Roentgenograms showed a fracture of the L 3 vertebral body with horizontal splitting of the right pedicle and both transverse processes into 2 parts (Fig. 1, A and B).

In the first 24 hour period the abdomen became distended and painful. Roentgenograms showed free intraperitoneal air, and a "gastrografin" swallow revealed contrast material extending outside of the upper jejunal loops, at the site of perforation (Fig. 1, C and D). There also was a superficial laceration of the cecum, but no other intraabdominal injury. The vertebral fracture was treated with hyperextension body cast, and there was complete recovery, except for residual back pain with exercise.

Case 2. This 20 year old man, a passenger in the front seat, was wearing a lap seatbelt at the time of head-on collision. Two people in the rear of the automobile were thrown against the back of his seat, and as he flexed over the seatbelt his face struck the rear view mirror. There was a large contusion of the left abdomen underlying the seatbelt, and there was a large circular area of edema at the L 3 level on the back.

Roentgenograms revealed a compression fracture of the body of L 3 with horizontal extension through the pedicles and transverse processes (Fig. 2, A and B). There were extensive facial fractures involving the orbital floors, and a surgical procedure to reduce the depression of the floor of the right orbit was done several days later. There were 2 later operative procedures performed in the facial region, using graft material. Recovery was complete except for some continuing back discomfort with exercise.

Case 3. A 20 year old college student was a front seat passenger wearing a seatbelt, when a front-side automobile collision occurred. She struck the dashboard and received a bruise about the right eye. There was no abdominal injury except for a "seatbelt contusion." In the emergency room she complained of back pain, and a localized area of edema was noted over the upper lumbar region.

Roentgenograms showed slight compression of the vertebral bodies of L I and L 2. The L I fracture extended posteriorly through the pedicles and transverse processes (Fig. 3, A and B). The patient was treated with a Jewett brace at the time of discharge from the hospital 2 weeks following the accident.

Case 4. This 18 year old female was a passenger in the right front seat with her seatbelt securely fastened at the time of a head-on collision with another automobile. There were multiple facial lacerations and a fracture of the L 2 vertebra, with slight compression of the anterior body and horizontal extension of the fracture through both pedicles and both transverse processes (Fig. 4, A and B).

On the following day, a four-quadrant tap was negative for blood, but an exploratory laparotomy was done because of the acute nature of her abdominal signs and symptoms. There were several superficial serosal tears found in the mesentery and small bowel, and a small retroperitoneal hematoma was found at the L 2 level, at the site of fracture. No actual perforation of bowel or other injury was discovered.

One week after admission, surgical exposure of the lumbar area revealed an extradural hematoma and a small tear of the dura at the L 2 level, along with a laceration of a dural root sleeve. A spinal fusion was done and the patient was later treated with a body cast, with satisfactory recovery.

#### DISCUSSION

From our 10 cases and a review of the literature, it is evident that seatbelts can produce serious injury to the spine and abdomen. The patterns of lumbar spine injury have been illustrated by Smith and Kaufer<sup>21</sup>; the acute flexion over the seatbelt produces a tearing and separation of the posterior elements, either osseous or ligamentous structures, or both. The pos-

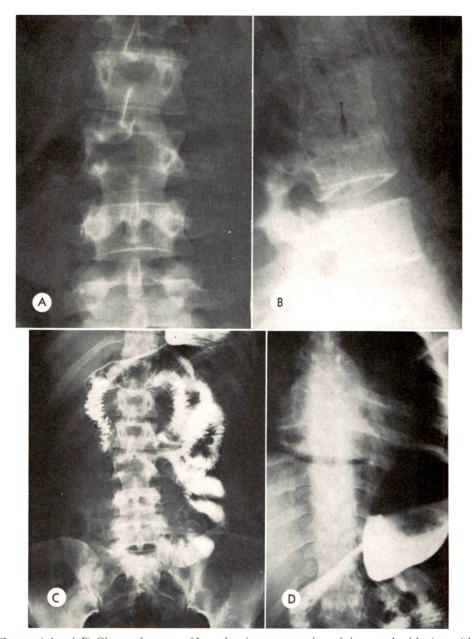


Fig. 1. Case 1. (A and B) Chance fracture of L 3, showing compression of the vertebral body and horizontal splitting of the right pedicle and transverse process. There is a hairline fracture of the left transverse process, and separation of the L 2-3 facets on the left. (C and D) Flat and upright abdominal roentgenograms after gastrografin swallow, showing free air, and contrast material outside the loops of proximal jejunum.

terior tearing and separation may be rather minor, as in Case 8; or it can be quite extensive with complete dislocation of the spinal column, with paraplegia. The Chance lateral flexion will account for the variable fracture is one of the intermediate forms between the 2 extremes; the variations of

this type of fracture are illustrated in Figures 1 through 6. The vertebral body compression may be minimal. Degrees of unilateral or bilateral involvement of the posterior arch. If the spinous process is not

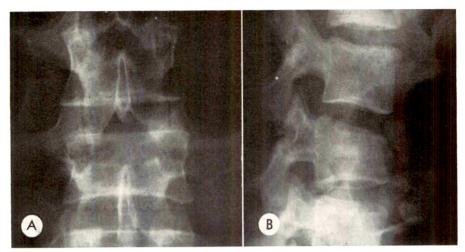


Fig. 2. Case 2. (A and B) Horizontal Chance fracture of L 3 which is quite symmetric. Note the separation of the spinous processes.

torn apart, there is then a complete rupture and tearing apart of the interspinous and supraspinous ligaments. A Chance fracture of a vertebra has been described as unique to a seatbelt injury; however, it is conceivable that acute flexion of the torso over some other fixed object could result in a similar fracture.

Good quality roentgenograms of the area

of spinal injury are necessary to demonstrate the extent of these fractures. We have found anterior tomograms (Fig. 5, B-D; and 6, C and D) of the spine quite useful to demonstrate the precise extent of the fractures of the posterior elements.

It should be noted that the history of injury associated with the seatbelt is usually *not* given by the clinician—he may not

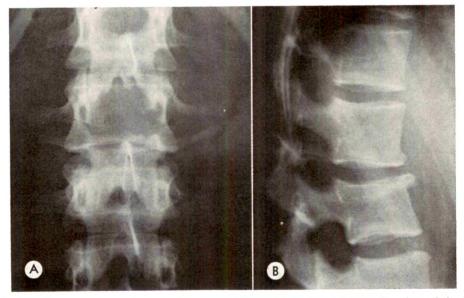


Fig. 3. Case 3. (A and B) Typical Chance fracture of L 1, with horizontal extension through both pedicles and transverse processes. There is separation of the spinous processes of D 12 and L 1, indicating rupture of the interspinous ligament. There is slight compression of the bodies of L 1 and L 2. (The D 12 vertebra has no ribs.)

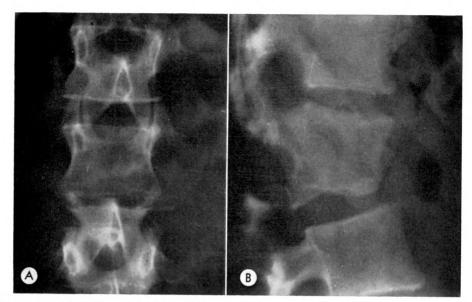


Fig. 4. Case 4. (A and B) Chance fracture of L 2 with slight compression of the anterior corner and avulsion of the posterior corner of L 2 body. Note the wide separation of the pedicle and transverse process fragments.

know that the patient was wearing a seatbelt, or may not be aware of its importance. In most of our cases the typical fracture was seen on roentgenograms, and afterward the relationship with the seatbelt was established after direct questioning of the patient and examination of the anterior abdominal wall for a seatbelt contusion.

Any patient with a seatbelt fracture of the spine must be observed closely for an intraabdominal injury, and the reverse is also true. There have been at least 20 reported cases of seatbelt fracture of the spine and serious intraabdominal injury occurring together; there are 3 combination spine-and-abdominal injuries in our 10 patients. The radiologist should be aware that the usual injury involves the small bowel and its mesentery; but almost any other abdominal organ can be involved, and multiple injuries are quite common.

It is difficult to recognize free air in the peritoneal cavity in those cases of small bowel perforation. In the majority of cases in the literature, free air was not seen on roentgenograms. Water soluble contrast media are useful in helping demonstrate some of these perforations, as in Case 1.

Several authors emphasize early exploratory laparotomy in these patients because of the insidious nature of small bowel perforation when superimposed upon other major injuries.<sup>6,10,17,23</sup>

Backwinkel<sup>1</sup> and Sube *et al.*<sup>23</sup> have discussed the major factors producing injury to the spine and abdominal contents: (1) compression of the intraabdominal organs between the belt and vertebra; (2) acute flexion over the belt fulcrum; and (3) a sheering or inertial force on fluid-filled loops of bowel. Special note is made of the highly unusual cases of "sleeve stripping" of the large bowel, in which the mesentery, serosa, and muscular layers are completely torn away from the intact tube of mucosa. The mechanism of injury in these cases has not been satisfactorily explained.

Several reports in the literature relate abdominal injuries to improperly fastened seatbelts: seatbelts too loose, or too highly placed around the abdomen, rather than around the pelvic structures.<sup>8,12,13,23</sup> However, there is a considerable number of cases, including most of our own, in which the seatbelt was tightly fastened in the usual position around the pelvis; and

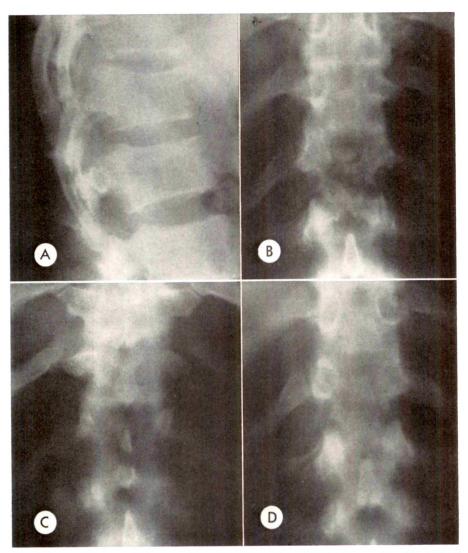


Fig. 5. Case 5. Chance fracture of D 12; atypical fracture of L 1. (A) Slight compression of bodies of D 12 and L 1. (B and C) Anteroposterior tomograms showing fracture of the lamina of D 12, and splitting of the spinous process. (D) Anteroposterior tomogram showing fracture of the right transverse process of L 1. Posterior arch otherwise intact.

it is obvious that even a properly positioned lap seatbelt can produce a serious injury.

The diagonal seatbelt, used alone in automobiles in Europe for many years, has been known to produce fractures of the ribs and sternum, as well as injuries to the upper portion of the abdomen with laceration of liver, spleen, or kidney.<sup>7,8,15,20</sup> There have been 2 reported cases of complete decapitation which occurred during ejection of the driver using the diagonal belt alone.<sup>18</sup> Standards for Swedish safety belts

have recently been changed in favor of a combined diagonal and lap belt.<sup>20</sup>

The recent report by Hamilton<sup>11</sup> describing 3 patients severely injured while using combination lap-and-diagonal belts is rather disheartening. Not only were there severe injuries of the abdominal viscera, there were flexion-compression fractures of the cervical-dorsal junction in 2 patients. The author speculates on the possibility of increased incidence of neck and upper spine trauma using the combination belt.

It would appear, from a review of injuries produced by lap and combination lap-and-diagonal belts, that a full shoulder harness and lap belt would be the most satisfactory restraining device. The use of headrests, improved door and seat construction, and perhaps the new "air bag" mechanism, will also help prevent serious

injury to those involved in a serious automobile crash.

#### CONCLUSIONS AND SUMMARY

Although the safety value of automobile seatbelts has been proven, the seatbelt is capable of producing serious injury to the spine and intraabdominal contents during

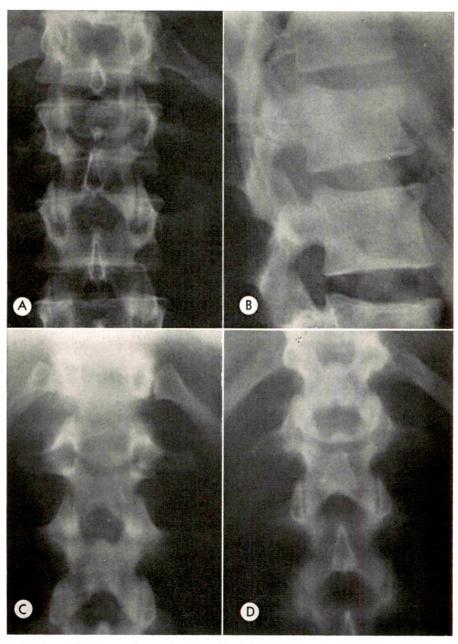


Fig. 6. Case 6. (A and B) Chance fracture of L i. (C and D) Anteroposterior tomograms demonstrate the posterior extension through the pedicles, transverse processes, and spinous process.

an abrupt deceleration crash. Ten cases of injury to the spine, pelvis, and abdomen are added to the expanding literature on seatbelt injuries.

At least 40 cases of serious injury to the spine have been reported with the lap seatbelt. The trauma to the spine is produced by severe flexion of the torso over the belt, causing a tearing of the posterior elements, with less involvement of the vertebral bodies. One of the interesting intermediate forms of vertebral injury is the Chance fracture: a horizontal splitting and separation of the posterior vertebral arch, involving the pedicles, lamina, transverse processes, and spinous process, with variations.

Following seatbelt trauma to the abdomen, the most common injury is perforation of the small bowel with associated trauma of its mesentery. Injury to almost every hollow and solid viscus in the abdomen has been reported, and multiple injuries are common. Combined injuries of the spine and intraabdominal contents occur.

Knowledge of the type of injury produced by seatbelts will lead to more prompt and accurate diagnosis of the extent of injury. The history of flexion over the seatbelt, or the observation of a seatbelt contusion, is most important. Good quality roentgenograms of the spine in multiple projections, and occasionally tomograms, are of great value. Oral water soluble contrast media can be helpful in the diagnosis of intestinal perforation, since free air is difficult to demonstrate in these seriously ill patients.

The diagonal belt and the combination lap-and-diagonal belt have produced injury to the sternum, ribs, and upper abdomen. The diagonal belt prevents the lumbar flexion fracture seen with the lap belt, but may produce a flexion type injury in the neck. The shoulder harness used with the lap belt should be evaluated to replace the lap-and-diagonal belt, along with other structural improvements in automobile safety design.

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# THE ROENTGENOGRAPHIC APPEARANCE OF TRANSVERSE OR CHANCE FRACTURES OF THE SPINE: THE SEAT BELT FRACTURE\*

By LEE F. ROGERS, M.D.†

TN 1948, Chance<sup>3</sup> described an unusual fracture of the vertebral body consisting of a "horizontal splitting of the spine and neural arch, ending in an upward curve which usually reaches the upper surface of the body just in front of the neural foramen." In his 3 cases, there was very little wedging of the vertebral body. With the advent of the automobile lap-type seat belt in the 1950s and its general acceptance and common usage in the 1960s, the Chance fracture has been found with increasing frequency as a result of injuries sustained while wearing the lap-type seat belt. Howland et al.,5 in 1965, reported a case of a complete transverse fracture of the 3rd lumbar vertebra in a 19 year old boy injured in an automobile accident while wearing a seat belt. The authors theorized that "this injury was produced by the seat belt acting as a fulcrum over which the vertebral body was split transversely into 2 parts." The fracture was termed a fulcrum fracture of the lumbar spine. This theory was refined by Smith and Kaufer. In the usual hyperflexion injury of the spine, the compression forces generated are sustained by the anterior half of the vertebral body, thus resulting in a wedge or compression fracture of the vertebral body. With the wearing of a seat belt the fulcrum of the force is displaced anteriorly and lies at the seat belt. The entire spine is, therefore, posterior to the flexion axis and all of its components are subjected to tension stress. This results in a disruption of the ligaments of the posterior elements of the spine or, should the ligaments remain intact, a transverse or fission type fracture of the posterior elements and, at times, the vertebral body. This

same pattern has been seen without the use of a seat belt as a result of injuries in which the individual either fell or was thrown forward so that the anterior abdominal wall came in contact with some object, *i.e.*, tree limb or fence railing. This object serves as a fulcrum in a manner similar to a seat belt and forces the body into acute flexion.

The usual flexion compression fracture of the spine involves either the twelfth dorsal or first lumbar vertebra. In contradistinction, the transverse fracture most commonly involves the first, second or third lumbar vertebra. In approximately 15 per cent of transverse fractures, there are associated intra-abdominal injuries. These consist chiefly of tears of the mesentery, ruptures of the small bowel, and/or lacerations of solid organs. Another 15 per cent are associated with injuries to the spinal cord or cauda equina.

#### PRESENT SERIES

Six transverse fractures of the spine were encountered in 5 individuals over the past 12 months. All injuries were in males, age 10 to 35 years. Three individuals were wearing a lap-type seat belt. All were deceleration injuries. Four of the five sustained intra-abdominal injuries. Two injuries resulted in paraplegia. Two of the fractures occurred in siblings wearing seat belts riding in the rear seat of an automobile. One was a unique case. This individual sustained 2 transverse fractures involving consecutive vertebrae, L3 and L4. The least injured individual was driving an automobile without a seat belt. He was thrown from the automobile, but the exact mechanism of his injury could not be as-

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Table I
6 fractures in 5 individuals (all survive)

Case	Age and Sex	Vertebra Involved	Seat Belt	Vehicle and Position	Abdominal Injury	Neural Defici
I. CL	35 Male	Lı	No	Automobile Driver	None	None
II. WY	16 Male	L3	No	Motorcycle	Rupture of 2nd and 3rd portion of duodenum, of pan- creas, and of middle colic artery	None
III. HC	14 Male	L.2	Yes	Automobile Back seat	Rupture of right rectus muscle, rupture of jejunum, serosal tears of colon	Paraplegia
IV. JC	10 Male	L <sub>3</sub>	Yes	Automobile Back seat	Rupture of jejunum	Paraplegia
V. LY	15 Male	L3, L4	Yes	Automobile Back seat	Rupture of abdomi- nal wall muscula- ture, tears of small bowel mesentery	None

certained. One was a motorcycle driver who ran into the side of an automobile crossing his path of travel. At impact he was "folded" or flexed over the motorcycle gas tank which had been torn free of its attachments. In essence, the mechanism of his injury was similar to that with the use of a seat belt. The pertinent clinical features are summarized in Table 1.

#### ROENTGENOGRAPHIC APPEARANCE

On viewing roentgenograms of the abdomen or lumbar spine obtained for the evaluation of traumatic injuries, the eye is attuned to search for the loss of vertebral body height indicating a compression fracture of the spine.<sup>2</sup> The status of the posterior elements receives scanty or little particular attention. The key to the recognition of transverse fractures, however, rests with the appearance of the posterior elements of the vertebral body. It is particularly important to be aware of their appearance on the anteroposterior view of the abdomen or lumbar spine. This is true for

two reasons. Firstly, because of the critical status of many patients in the immediate postinjury period, only an anteroposterior view may be obtained; and secondly, the posterior elements of the spine are insufficiently visualized for evaluation in many lateral views of the abdomen or lumbar spine obtained under the circumstances. On the anteroposterior view of the lumbar spine, the cortical margins of the spinous processes are tear-shaped and the cortical margins of the pedicles are ovoid. The lamina, transverse processes and articular processes are solid plates of bone. The inferior articular facets are well seated within the superior articular facets of the adjacent inferior vertebral body.

The fulcrum-type force creates either ruptures of the posterior ligaments and facet joints or fractures of the posterior elements and vertebral body, or varying combinations of ligamentous rupture and fracture. There are 3 basic patterns resulting from fulcrum-type injuries of the spine:

I. A disruption of the posterior spinous

ligaments, articular facets and the intervertebral disks. There may be an associated avulsion of an articular facet or posterior inferior aspect of the vertebral body. The pedicles, spinous and transverse processes remain intact.

- 2. Transverse fracture involving the posterior elements with or without extension into the posterior superior or posterior inferior aspect of the vertebral body. The fracture line may involve one or both pedicles, transverse processes, articular facets as well as the lamina and spinous process.
- 3. Transverse fracture of the posterior elements with an associated transverse fracture of the vertebral body. This fracture involves the spinous process, lamina, pedicles and usually the transverse processes.

In the frontal projection, there are two clues to the recognition of this injury. With either a transverse fracture of the posterior elements or a disruption of the ligaments there may be sufficient angulation of the superior fragment or vertebra so that a portion of the vertebral body is no longer overlaid by the posterior elements. This separation and elevation of the posterior elements gives rise to an empty or vacant

appearance of the vertebral body involved (Fig. 2, A and B; 3, A and B; and 5, A and B). Another key to the discovery of this injury lies in the recognition of a break in the continuity of the oval-shaped cortex of the pedicles and/or tear-shaped cortex of the spinous process (Fig. 1–5). One may also visualize the fracture line within the lamina or articular processes. A transverse fracture of the transverse process creates an unusual bifid appearance of this structure (Fig. 5, A and B).

Confirmation rests with an adequately exposed and properly positioned lateral film of the lumbar spine. If properly exposed, the line of fracture within the spinous process, pedicles and vertebral body is readily identified (Fig. 1, A and B). If a pure ligamentous rupture has occurred, anterior angulation of the superior vertebra with a separation of the posterior elements is demonstrated. Should the posterior elements be poorly defined because of overexposure or improper positioning, an avulsion fracture or irregularity of the posterior aspect of the superior or inferior plate of the vertebral body and/or anterior angulation are clues (Fig. 3, A and B; and A, A and B). Should such a

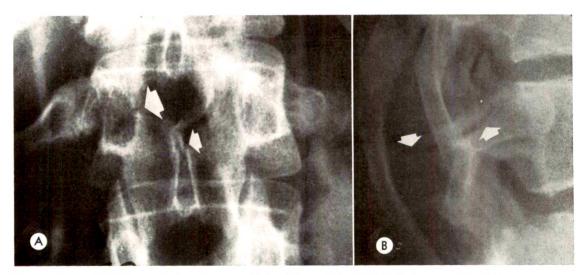


Fig. 1. Case 1. (A) The oval-shaped cortex of the right pedicle ( and the tear-shaped spinous process ( ) of L1 are disrupted. The fracture line is identified within the left lamina. (B) The fracture of the spinous process ( ) is confirmed. No angulation is present. The fracture extends into the posterosuperior aspect of the vertebral body. The latter is not easily seen in this view.

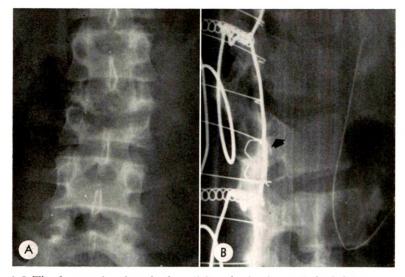


Fig. 2. Case II. (A) The fracture involves both pedicles, the lamina and the left transverse process of L<sub>3</sub>. The separation gives an empty appearance to the vertebral body. This might be misinterpreted as gas within the bowel. (B) The initial lateral roentgenogram obtained on a stretcher reveals a disruption of the posterior superior aspect of the vertebral body. The fracture extends through the pedicles ( into the vertebral body.

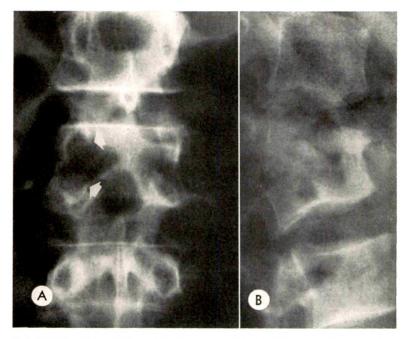


Fig. 3. Case III. (A) The fracture of L2 involves both pedicles ( and transverse processes, the lamina and spinous process. The widely separated fragments give rise to an empty or vacant appearance of vertebral body. (B) Angulation is present at the fracture. Separation of the fragments of the pedicle is evident. The fracture extends through the inferior plate of the vertebral body. Minimal compression of the anterosuperior surface of the body is evident.

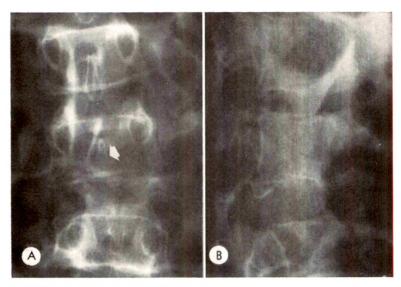


Fig. 4. Case IV. (A) The fracture involves the lamina, transverse processes, spinous process ( ) and inferior cortex of the pedicles. (B) The fracture of the pedicle is evident. It extends into the inferior posterior aspect of the vertebral body. Angulation is present.

fracture or angulation be present, the frontal view should be scrutinized and a lateral examination obtained with an appropriate exposure to demonstrate the posterior elements. One is then able to confirm the presence of a transverse fracture.

Characteristically, there is minimal compression of the vertebral body. When

present, it involves the anterior superior aspect (Fig. 3, A and B). Neither is there any degree of lateral displacement or rotation of the fracture fragments. Anterior displacement of the superior vertebral body or the superior fragment is unusual. When present, it is commonly associated with an injury to the spinal cord or cauda equina.

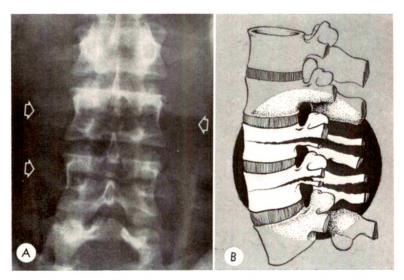


Fig. 5. Case v. (A) A unique case with transverse fractures of both L3 and L4 ( ). The pedicles, lamina and transverse processes are involved at both levels. The separation is more marked at L3. (B) Tracing demonstrating the transverse fracture of the vertebral bodies at both levels.

#### DISCUSSION

No author attempts to discredit the seat belt or imply that more injuries are created than prevented by its use. The best estimate, given by Tourin and Garrett,<sup>10</sup> is that fatal and severe injuries are reduced by about 35 per cent through the use of the seat belt. For the most part, the internal injuries associated with their use are not unique, but are encountered in all forms of blunt abdominal trauma.

The phrase "Seat Belt Syndrome" was first coined by Garrett and Braunstein<sup>4</sup> in 1962. It designates those injuries frequently encountered in individuals injured while wearing a lap-type seat belt.8 Typically, the individual affected is a passenger, either in the front or back seat, and is involved in a head-on collision resulting in sudden deceleration at impact. The impact speed frequently exceeds 50 miles per hour. The syndrome consists of one or more of the following injuries: transverse abrasions of the lower anterior abdominal wall outlining the position of the seat belt at the time of impact; ruptures of the anterior abdominal wall musculature; longitudinal lacerations of the small bowel, "particularly on the antimesenteric border of the jejunum and ileum; tears of the mesentery;11 ruptures of the 2nd or 3rd portion of the duodenum, spleen, or pancreas; injuries to the cauda equina or spinal cord; and transverse fractures of the lumbar spine. Rupture of the gravid uterus has been reported.6 A peculiar circumferential avulsion of the outer layers of the sigmoid colon leaving the mucosa intact has been described.<sup>1,9</sup>

The treatment of transverse fractures varies with the amount of separation of the fracture fragments. If there is no associated abdominal injury, treatment in a hyperextension cast is adequate in most cases. Occasionally, an open reduction and stabilization is deemed necessary.

#### SUMMARY

Chance first described the transverse fracture of the spine in 1948. They were rarely encountered before the general use

of the lap-type seat belt. The fracture is created by an acute flexion of the body over or against some object which serves as a fulcrum. This mechanism creates ruptures of the posterior ligaments, fractures of the posterior bony elements or some combination of both.

The roentgenographic features of various combinations of injuries are presented. The importance of their recognition and the appearance of these injuries on the anteroposterior roentgenogram are stressed.

The author's experience with 6 fractures in 5 patients is reviewed.

The "Seat Belt Syndrome" is discussed.

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## M E D I T O R I A L S M

## BRAIN SCANNING—IS IT BECOMING UNNECESSARILY COMPLICATED?

FOUR or five years ago a 4-view brain scan (anterior, posterior, and both lateral views) would have been routine in most large centers. The tracer used would probably have been pertechnetate 99m, and the accuracy of detection would have been about 85 per cent for brain tumors. Irradiation of the patient was low, and the examination time of 1/2 to 1 hour short enough to permit all referred patients ready admission to the daily schedule without undue delay. With these credentials, the brain scan became a key screening procedure and occasionally the study of diagnostic impact.

Recently, newer tracers such as technetium 99m albumin, technetium 99m DTPA, and indium 113m DTPA have been suggested as alternatives. Nuclide dynamic studies (i.e., nonselective nuclide cerebral angiographies done on stationary detector systems) have been introduced; additional views such as vertex views, orbital views (frontal view with the chin extended), or special posterior fossa views have been described; and delayed scanning of up to 4 hours has been advocated. With little effort such "progress" can push brain scanning beyond all practical limits. If, for example, we concede that virtually all nuclide comparisons conclude that "both agents are better than either alone," and that all four of the examination procedures (dynamic, routine, adjunctive, and delayed scans) have some merit, then a two-tracer-fourvariable brain scan (assuming about 1/2 hour for each part of the study) will take four hours to complete; i.e., only 3 patients can be examined per 12 hour day. Since many lesions are not visualized because they do not have a high enough uptake of any routine nuclide regardless of circumstances, it is clear that all of these maneuvers will still fail to be diagnostic. No one as yet knows what the ultimate diagnostic possibilities are, but it is *doubtful* whether more than 90 per cent of all brain tumors can be detected with today's nuclides and equipment. In short, with a maximum of effort we can expect but a minimum gain. In fact, in many centers, the brain scanning time is now so long and the demand so great as to cause scheduling delays that could result in a *decrease* in the number of patients examined which might even *negate* the diagnostic improvement.

There is no easy solution to this increasingly difficult problem, but I would like to present a philosophic approach that has helped us at the University of Chicago Hospitals as an example of what can be done. We have virtually abandoned the concept of a routine brain scan, and try instead to tailor each study to the individual case. Although we have gamma cameras, we do not obtain a nuclide angiogram on everyone, but tend to reserve this study for those suspected of a vascular problem (e.g., CVA, subdural hematoma, or A-V malformation). About 15 minutes after injection (we still use pertechnetate 99m), we try to get the "routine" 4 views on our ACRH brain scanner,1 (unless the patient is critically ill, when we use a camera to get the views that are possible without moving the patient from his hospital stretcher). At this point the scans are monitored. If there is a sus-

<sup>1</sup> Gottschalk, A., Abatie, J. D., Petasnick, J. P., Polcyn, R. E., Beck, R. N., and Charleston, D. B. ACRH brain scanner. Comparison between sensitivity and resolution based on a clinical evaluation. In: Medical Radioisotope Scintigraphy. Vol. II. IAEA, Vienna, 1968, pp. 563–575.

picious region, the necessary additional studies such as vertex or delayed views are obtained. In addition, since it is known that some lesions (especially metastases) are visible only on delayed views, we may be governed by the patient's disease and symptoms even though the examination is normal up to that time. Even then, however, we may not do a "comprehensive" study, but only the study considered relevant. If a subject suspected of metastases, for example, has a right hemiparesis and a normal 4-view study completed at I hour, and the delayed (3-4 hour) left lateral view is normal, we stop without obtaining the delayed frontal, posterior and other lateral views. In short, the physician in charge makes appropriate selective medical judgments based on the examination as it unfolds before him in conjunction with the patient's signs and symptoms.

Clearly this approach depends upon the good judgment of the physician monitoring the study. Since this is a teaching hospital, most of our cases are monitored by residents or junior staff members who may in fact overlook some aspect of the study ultimately deemed desirable by supervisory staff at regular review. When this happens, we have no hesitation in recalling the patient for a repeat examination. On occasion, this may even improve the study. A nuclide angiography, for example, might be done in posterior or lateral position because

the lesion has already been localized. The dose to the patient from an additional 10–12 mc of pertechnetate 99m is low, and is quite comparable to recalling a patient for a repeat gastroduodenal examination.

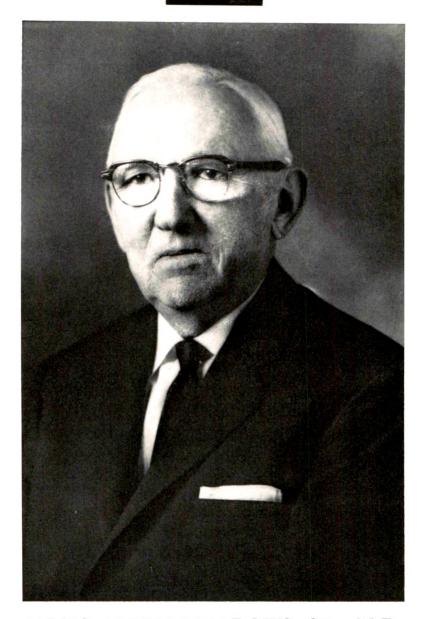
In conclusion, I firmly believe that it is no longer efficacious for the nuclear radiologist to try to do "everything" on each brain examination. At the same time it is wrong to expect the technologist to decide which "routine" is to be followed. Brain scanning has reached a stage where selective medical judgment is important, and each study should be planned and monitored by the physician. To do this effectively, a radiologist must be familiar with both his equipment and his patient.

If provision is not made to adopt this "appropriate" rather than "complete" brain examination, the ever increasing demand will inundate the nuclear laboratory and seriously compromise the delivery of good radiologic health care.

Alexander Gottschalk, M.D. President, Association of University Radiologists

Department of Radiology (Section of Nuclear Medicine), The University of Chicago, and the Argonne Cancer Research Hospital (operated by the University of Chicago for the United States Atomic Energy Commission) 950 East 59th Street Chicago, Illinois 60637





JAMES ALLEN MEADOWS, SR., M.D. 1884–1970

ON JUNE 3, 1970, Dr. James Allen Meadows, Sr. died of coronary artery disease at the age of 86 years.

Dr. Meadows was born in 1884 in Quitman, Mississippi. He moved to Birmingham, Alabama, in 1905 to attend business school. Deciding to become a physician, he

entered Mobile Medical College in 1910 and was graduated in 1912. Dr. Meadows interned at St. Vincent's Hospital, Birmingham, Alabama, and then spent one year in pathology at Touro Infirmary, New Orleans, Louisiana. In 1915 he went to Mayo Clinic to study Radiology under Dr. Russell

D. Carman. He returned to Birmingham and started his practice in radiology at St. Vincent's Hospital, being the first radiologist in Alabama. He remained closely associated with St. Vincent's Hospital until his retirement at the age of 80. He served as Chief of Radiology for St. Vincent's Hospital, South Highland's Infirmary, Highland Baptist Hospital, West End Baptist Hospital, The Children's Hospital and as Consultant in Radiology to the Crippled Children's Clinic. He was the first radiologist to offer services to the Jefferson County Antituberculosis Association. The first roentgen-ray therapy and cobalt 60 teletherapy units in Alabama were installed in his private office.

Dr. Meadows was a Fellow in The American College of Radiology, a member of the American Medical Association, Alabama State Medical Association, American Roentgen Ray Society, The Radiological Society

of North America, The Jefferson County Medical Society, of which he was a former President of the Birmingham Surgical Society, and the Birmingham Clinical Club.

His practice is continued by his two sons, James Allen Meadows, Jr., and Edward Russell Meadows, and their associates. His daily trips to the office and hospitals to see his associates and friends will be missed by all. He befriended many in his quiet humble way and was often consulted by other radiologists for advice and counsel. His enthusiasm for progress never waned and he always encouraged his associates to try new equipment and ideas.

Dr. Meadows is survived by his widow, Minna M. Meadows, two sons and a daughter.

James A. Meadows, Jr., M.D. Edward R. Meadows, M.D.

201 Medical Arts Building Birmingham, Alabama 35205



## TENTH INTER-AMERICAN CONGRESS OF RADIOLOGY

THE Tenth Inter-American Congress of Radiology will be held at the San Jeronimo-Hilton Hotel in San Juan, Puerto Rico, May 16–22, 1971. A detailed account of the attractive social activities, which have been arranged by President Victor A. Marcial, M.D., and his untiring Committees on the occasion of this Congress, was given in the February 1971 issue of this Journal (pp. 424–425).

The following is a description of the main items of the outstanding Scientific Program. The day of Wednesday, May 19, 1971 was left free so that members of the Congress and their guests may have the unique opportunity of visiting, in a pleasant tropical climate, the rare treasures of old and new San Juan and of witnessing the tremendous accomplishments that have been achieved.

## PRELIMINARY SCIENTIFIC PROGRAM

#### I. RADIODIAGNOSIS

Monday, May 17, 1971.

Chairman: Dr. Jorge Ceballos, (Méjico) 8:30 A.M.-11:30 A.M. Radiology of Parasitic Diseases

11:30 A.M.—12:30 P.M. Proffered Papers Chairman: Dr. Elias G. Theros, (U.S.A.) 1:30 P.M.—4:30 P.M. Radiology of Bone Diseases 4:30 P.M.—5:30 P.M. Proffered Papers

#### Tuesday, May 18, 1971.

Chairman: Dr. Clifton B. Harris, (U.S.A.) 8:30 A.M.-11:30 A.M. Pediatric Radiology 11:30 A.M.-12:30 P.M. Proffered Papers Chairman: Dr. Manuel Viamonte, Jr., (U.S.A.) 1:30 P.M.-4:30 P.M. Cardiovascular Radiology 4:30 P.M.-5:30 P.M. Proffered Papers

#### Thursday, May 20, 1971.

Chairman: Dr. Juan M. Taveras, (U.S.A.) 8:30 A.M.—II:30 A.M. Neuroradiology II:30 A.M.—II:30 P.M. Proffered Papers Chairman: Dr. Gonzálo Esguerra Gómez, (Colombia)

1:30 P.M.-4:30 P.M. Radiology of the Gastrointestinal Tract

4:30 P.M.-5:30 P.M. Proffered Papers

Friday, May 21, 1971.

Chairman: Dr. Benjamin Felson, (U.S.A.) 8:30 A.M.-II:30 A.M. Radiology of the Chest II:30 A.M.-I2:30 P.M. Proffered Papers Chairman: Dr. Richard Freidenberg, (U.S.A.) I:30 P.M.-4:30 P.M. Radiology of the Genitourinary Tract 4:30 P.M.-5:30 P.M. Proffered Papers

Saturday, May 22, 1971.

Chairman: Dr. Lucy Frank Squire, (U.S.A.) 9:30 A.M.-12:00 A.M. Education in Radiology

#### II. RADIOTHERAPY

Monday, May 17, 1971.

8:30 A.M.—11:00 A.M. Proffered Papers
11:00 A.M.—12:30 P.M. Optimal Radiation Therapy
of Carcinoma of the Cervix—Symposium
Dr. José Noriega Limón, Presiding
Dr. Gilbert H. Fletcher, Dr. Francisco Tenorio,
Dr. Fernando Bloedorn, Dr. Jorge Carranza,
Dr. Antonio Bosch

12:30 P.M.-I:00 P.M. Electron Therapy of Cancer-Lecture

Dr. Norah duV. Tapley

2:30 P.M.-4:00 P.M. Management of Pediatric Tumors-Panel

Dr. G. D'Angio, Presiding

Dr. Audrey Evans, Chemotherapy; Dr. David Baker, Pediatric Surgery; Dr. R. Devek Jenkin, Radiation Therapy

4:00 P.M.-4:30 P.M. Computers in Radiation Therapy-Lecture

Dr. William Powers

#### Tuesday, May 18, 1971.

8:30 A.M.-II:00 A.M. Proffered Papers

11:00 A.M.—12:30 P.M. Interaction of Irradiation and Surgery in the Management of Head and Neck Cancer—Symposium

Dr. William Powers, Presiding

Dr. Morris Wizenberg, Dr. Luis Vallecillo, Dr. Frank Hendrickson

12:30 P.M.-1:00 P.M. Radiotherapy in the Management of Urinary Tract Tumors-Lecture Dr. Juan A. del Regato

2:30 P.M.-4:00 P.M. Management of Hodgkin's Disease-Symposium

Dr. Ralph Johnson, Presiding

Dr. Henry Kaplan, Dr. John Ultmann, Dr. Thomas Frei

4:00 P.M.-4:30 P.M. Split-Course Radiation Therapy of Cancer-*Lecture*Dr. Victor A. Marcial

Thursday, May 20, 1971.

8:30 A.M.-II:00 A.M. Proffered Papers

11:00 A.M.-12:30 P.M. Irradiation Combined with Chemical Agents in the Treatment of Cancer-Symposium

Dr. Raúl Vera, Presiding

Dr. Gilbert H. Fletcher

Dr. John Ultmann, Dr. Robert Lindberg, Dr. Morton Kligerman, Dr. Simon Kramer

12:30 P.M.-I:00 P.M. The Role of Radiation Therapy in the Curative Management of Carcinoma of the Breast–*Lecture* 

2:30 P.M.-4:00 P.M. Radiobiology for Radiation Therapists-Symposium

Dr. Herman Suit, Presiding

Dr. John F. Fowler, Dr. Eric Hall, Dr. Rodney Withers

4:00 P.M.-4:30 P.M. Status of Oxygen As an Adjuvant to Radiotherapy of Cancer-Lecture Dr. William Rider

Friday, May 21, 1971.

8:30 A.M.-II:00 A.M. Proffered Papers

11:00 A.M.-12:30 P.M. Anoxia in Radiotherapy-Symposium

Dr. Herman Suit, Presiding

Dr. Rodney Withers, Dr. Eric Hall, Dr. Richard Steckel

12:30 P.M.-I:00 P.M. Neutron Therapy of Cancer-Lecture

Dr. Jack Fowler

2:30 P.M.-4:00 P.M. Upper Abdominal Irradiation— Symposium

Dr. Philip Rubin, Presiding

Dr. Luther Brady, Dr. Julian Bloom, Dr. Melvin Griem

Saturday, May 22, 1971.

9:00 A.M.-12:30 P.M. Proffered Papers

12:30 P.M. Closing Ceremony

III. NUCLEAR MEDICINE

Monday, May 17, 1971.

8:30 A.M.-10:00 A.M. Thyroid-Panel

Dr. W. Beierwaltes, Dr. W. Blahd, Dr. H. M. Forcher, Dr. E. Otero Ruíz

10:15 A.M.-I:00 P.M. Proffered Papers

2:30 P.M.-4:00 P.M. Renal Function-Refresher Course

Dr. M. D. Blaufox

Tuesday, May 18, 1971.

8:30 A.M.—10:00 A.M. Lung Scanning—*Panel* Dr. H. N. Wagner, Dr. A. Gottschalk, Dr. V. López-Manjano

10:15 A.M.-12:30 P.M. Proffered Papers

2:00 P.M.-2:30 P.M. Treatment of Hyperthyroidism with I<sup>131</sup>-Lecture

Dr. W. Beierwaltes

2:45 P.M.-3:15 P.M. Clinical Applications of the Whole-Body Counter–*Lecture* 

Dr. W. Blahd

3:30 P.M.-5:00 P.M. Proffered Papers

Thursday, May 20, 1971.

8:30 A.M.-10:00 A.M. Scanning of Brain and Subarachnoid Spaces-Panel

Dr. A. Gottschalk, Dr. D. E. Kuhl, Dr. H. N. Wagner, Dr. E. J. Touyá

10:15 A.M.-12:30 P.M. Proffered Papers

2:00 P.M.-2:30 P.M. Current Trends in Nuclear Medicine–*Lecture* 

Dr. W. Beierwaltes

2:45 P.M.-3:15 P.M. Tomoscanning-Lecture Dr. D. E. Kuhl

3:30 P.M.-4:30 P.M. Proffered Papers



# NATIONAL COUNCIL ON RADIATION PROTECTION AND MEASUREMENTS (NCRP)

## REPORT ON BASIC RADIATION PROTECTION CRITERIA

THE publication of new radiation protection standards was announced on January 26, 1971 by the National Council on Radiation Protection and Measurements (NCRP). NCRP Report No. 39, Basic Radiation Protection Criteria, was released at a Press Conference held in Washington, D. C.

The new report represents a revision and modernization of radiation protection standards formulated by the NCRP in 1954 and revised in 1957 and 1958. At the time of the last revision the NCRP undertook a continuing review of the whole state of knowledge of the effects of ionizing radiation on man, especially in respect to its influence on radiation exposure for the population and standards for occupational conditions. The new report represents the end product of this review.

The new report evidences the Council's recognition that a comprehensive theory of radiation protection is not possible at this time but that the present body of information can be used to support a reasonable, generalized system of protection standards. The recommendations set out in the report constitute the Council's attempt to formulate such a system. The report represents the Council's contribution to the informed public review process believed to be necessary before public understanding and approbation of any radiation protection standards are possible.

The basic radiation protection criteria set out in the report are intended for 3 areas of application: (1) to provide a contemporary and more or less uniform framework for more detailed recommendations

of the various NCRP scientific committees that deal with specific aspects of protection; (2) in conjunction with reports of other NCRP scientific committees, to provide guidance in radiation protection to all concerned legislative bodies, governmental agencies, practitioners of the healing arts and their technical associates, all branches of the nuclear industry, and laboratories, universities, their staffs and students; and (3) to contribute to the public understanding of the prudent use of radiation as a beneficial agent, although some slight risk may be associated with it.

Report No. 39 is divided into two parts: Part I, Background and Supporting Material; and Part II, Radiation Protection Standards.

Part I includes chapters on radiation and man, radiation exposure conditions that may require consideration, basic biological factors, specific radiation effects and manifestations of overexposure in adults.

Part II includes chapters on bases for radiation protection standards, specific protection concepts or standards, and dose limiting recommendations and guidance for special cases.

The new report was placed on sale by NCRP Publications immediately after its release. Individuals already on the NCRP Publications Standing Order List will receive copies of the new report automatically and be invoiced for their order. Others may purchase copies of NCRP Report No. 39, Basic Radiation Protection Criteria from NCRP Publications, P.O. Box 4867, Washington, D. C. 20008.

## **NEWS ITEMS**

## THE AMERICAN BOARD OF RADIOLOGY

Special Notice Regarding Change in Training Requirements

In line with the action taken by the American Medical Association to phase out the freestanding internship by July 1, 1975, The American Board of Radiology announces the following change in its training

requirements.

Candidates beginning their training in Radiology or one of its branches after June 30, 1971 will be required to have 4 years of approved postgraduate training. Three of these years must have been spent in a Department of Radiology approved by the Residency Review Committee for Radiology, representing The American Board of Radiology and the Council on Medical Education of the American Medical Association, as competent to provide satisfactory training, in Radiology or in one of its branches. The fourth year may be spent in similar training, in an approved internship, or in an approved residency in another specialty, and it may precede, follow or be interspersed with the training in Radiology.

This means that a candidate may be certified within 4 years after receiving his M.D. degree or its equivalent. A candidate who fulfills these requirements will be eligible for the written examination 3 years after graduation from medical school and, if he passes that examination, will be eligible for the oral examination 4 years after

graduation.

## CHEST RADIOLOGY POSTGRADUATE COURSE

Albert Einstein College of Medicine

The Department of Radiology of the Albert Einstein College of Medicine, Bronx, New York, will sponsor a Postgraduate Course in Chest Radiology from May 17 to May 21, 1971.

It is intended for radiologists and other physicians interested in diseases of the chest, and will include a review of present

day concepts of radiology of the respiratory tract. Film interpretation panels will emphasize the approach to diagnostic problems.

For further information, please contact Dr. Milton Elkin, Professor and Chairman, Radiology, Albert Einstein College of Medicine, Bronx, New York 10461.

#### SHORT COURSE ON LASER SAFETY

University of Cincinnati

The Medical Laser Laboratory and the office of Continuing Medical Education (CONMED) of the University of Cincinnati announces a special "Short Course" on safe laser use, so vitally needed today by those using lasers in the military, scientific, governmental, industrial, and medical fields, to be held August 2–6, 1971.

For further information please contact Mr. R. J. Rockwell, Course Director, Laser Laboratory, Children's Hospital Research Foundation, Cincinnati, Ohio 45229.

#### SEVENTH NATIONAL CANCER CONFERENCE

The National Cancer Conferences are held every 4 years to bring cancer research workers and clinicians together to learn of the progress made in the management of cancer and to assess the needs in the control of cancer.

The Seventh National Cancer Conference sponsored by the American Cancer Society and the National Cancer Institute will be held at the Biltmore Hotel, Los Angeles, California, September 27–29, 1972.

All members of the medical and related professions, research investigators and medical students are invited to attend this Conference. There is no registration fee. Pre-

registration is requested.

For further information please write to Sidney L. Arje, M.D., Coordinator, Seventh National Cancer Conference, c/o American Cancer Society, 219 East 42nd Street, New York, New York 10017.

### **BOOKS RECEIVED**

DICTIONNAIRE FRANÇAIS DE MÉDECINE ET DE BI-OLOGIE. En quatre volumes. Volume I: A-D. By A. Manuila, L. Manuila, M. Nicole and H. Lambert; with the collaboration of J. Hureau (anatomie), J. Polonovski (chimie biologique), and 350 specialists. Preface by M. G. Candau, Directeur général de l'Organisation mondiale de la Santé. Publication dates of the 4 volumes: I. October 1970; II. April 1971; III. October 1971; and IV. First Semester, 1972. Cloth. Pp. 865. Price: by subscription. Before October 31, 1970 the subscription for the 4 volumes was fixed at 1,000 F.; after that date, the subscriber will be informed of the new terms and will receive the volume(s) which appeared previously. Masson & Cie. 120 Boulevard Saint-Germain, Paris 6, France, 1970.

MEASUREMENT OF CARDIAC CHAMBER VOLUMES AND DIMENSIONS BY RADIOGRAPHIC METHODS: A METHODOLOGICAL STUDY WITH SOME PHYSIOLOGICAL APPLICATIONS. By Erik Carlsson, Department of Radiology and the Cardiovascular Research Institute, University of California, San Francisco, Calif. Paper. Pp. 24, with many illustrations. Price, \$3.00. University of California Printing Department, Berkeley, Calif., 1970.

Intraosseous Spinal Venography. By Heinzgeorg Vogelsang, Head, Department of Neurology, The Clinical Centre, Lemgo/Lippe; and Lecturer in Clinical Neuroradiology, Justus Liebig University, Giessen, Federal Republic of Germany. Cloth. Pp. 117, with many figures. Price, \$14.00. Excerpta

Medica, Amsterdam. Exclusive U. S. agents, Williams & Wilkins Company, Baltimore, Md. 21202, 1970.

LATE EFFECTS OF RADIATION. Proceedings of the Colloquium held at the Center for Continuing Education, The University of Chicago, Chicago, Ill., May, 1969. Edited by R. J. M. Fry and Douglas Grahn, Biological and Medical Research Division, Argonne National Laboratory, Argonne, Ill.; and Melvin L. Griem and John H. Rust, Department of Radiology, The University of Chicago, Chicago, Ill. Paper. Pp. 298, with some figures. Price, \$10.95. Van Nostrand Reinhold Company, Division of Litton Educational Publishing Inc., 450 West 33rd Street, New York, N. Y. 10001, 1970.

DIAGNOSTIC RADIOGRAPHY: A MANUAL FOR RADIOLOGIC TECHNOLOGISTS. By Glenda J. Bryan, M.S.R., Superintendent Radiographer, Bristol Royal Infirmary, Bristol, England. Cloth. Pp. 290, with some figures. Price, \$12.50. E. & S. Livingstone, Edinburgh. Exclusive U. S. agents, Williams & Wilkins Company, Baltimore, Md. 21202, 1970.

RÖNTGENKONTRASTMITTEL: CHEMIE-PHYSIOLOGIE-KLINIK. By Dozent Dr. Med. Habil. Reinhard Barke, Leiter der Röntgendiagnostischen Abteilung der Radiologischen Klinik der Karl-Marx Universität, Leipzig. Cloth. Pp. 290, with some figures and tables. Price, GM-48.60. VEB Georg Thieme Leipzig, Abstazabteilung, DDR-69 Jena, Villengang 2, 1970.



### **SOCIETY PROCEEDINGS**

#### MEETINGS OF RADIOLOGICAL SOCIETIES\*

#### United States of America

AMERICAN ROENTGEN RAY SOCIETY

Secretary, Dr. Ted F. Leigh, Emory University Clinic, Atlanta, Ga. 30322. Annual meeting: Sheraton Hotel, Boston, Mass., September 28-October 1, 1971.

AMERICAN RADIUM SOCIETY

Secretary, Dr. Jerome M. Vaeth, Saroni Tumor Institute, 1600 Divisadero St., San Francisco, Calif. 94115. Annual meeting: Mexico City, Mexico, March 15-18, 1971.

RADIOLOGICAL SOCIETY OF NORTH AMERICA

Secretary-Treasurer, Dr. Maurice Doyle Frazer, 1744 South Fifty-eighth St., Lincoln, Neb. Annual meeting: Palmer House, Chicago, Ill., November 28-December 3,

AMERICAN COLLEGE OF RADIOLOGY

Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill. Annual meeting: St. Louis, Mo., Chase-Park Hotel, March 30-April 3, 1971.

Section on Radiology, American Medical Association Secretary, Dr. Ted F. Leigh, Emory University Clinic, Atlanta, Ga., 30322. Annual meeting: Atlantic City, N. J., June 20-24, 1971. American Board of Radiology

Secretary, Dr. C. Allen Good. Correspondence should be directed to Kahler East, Rochester, Minn. 55001. Oral examinations will be held in the following cities

during the next 2 years: Bal Harbour, Fla., June 7-11, 1971, Americana Hotel; Dallas, Tex., Dec. 6-10, 1971, Statler-Hilton Hotel; Washington, D.C., June 5-9, 1972, Washington-Hilton Hotel; and Atlanta, Ga., Dec. 4-8, 1972, Sheraton-Biltmore Hotel.
Written examinations are scheduled in June of each

year in 13 large centers, and applications must be re-ceived in the Board Office before Sept. 30 of the year preceding the one in which the candidate wishes to be examined. The written examinations this year will be held on June 19, 1971.

Deadline for filing applications for any examination

in 1972 is September 30, 1971.
American Association of Physicists in Medicine Secretary, Leonard Stanton, Hahnemann Medical College. 230 N. Broad St., Philadelphia, Pa. 19102. Annual meeting to be announced.

AMERICAN SOCIETY OF THERAPEUTIC RADIOLOGISTS Secretary, Dr. Carl R. Bogardus, Jr., University of Oklahoma Medical Center, Oklahoma City, Oklahoma 73104 AMERICAN INSTITUTE OF ULTRASOUND IN MEDICINE

Secretary, F. J. Fry, M.Sc., Bioacoustics Lab., University of Illinois, Urbana, Ill.

American Society of Neuroradiology

Secretary-Treasurer, Dr. Eugene V. Leslie, Edward J. Meyer Memorial Hospital, 462 Grider St., Buffalo, N. Y. 14215.

THIRTEENTH INTERNATIONAL CONGRESS OF RADIOLOGY Meeting: Madrid, Spain, Oct. 13-19, 1973.

TENTH INTER-AMERICAN CONGRESS OF RADIOLOGY Counselor for the United States, Dr. Manuel Viamonte, Jr., University of Miami School of Medicine, Jackson Memorial Hospital, Miami Fla. 33136.

President, Dr. Victor A. Marcial, Puerto Rico Nuclear Center, Caparra Heights Station, San Juan, Puerto Rico

Meeting: San Jeronimo-Hilton Hotel, San Juan, Puerto Rico, May 16-22, 1971.

INTER-AMERICAN COLLEGE OF RADIOLOGY

President, Dr. Juan A. del Regato, Penrose Cancer Hos-

pital, 2215 North Cascade Ave., Colorado Springs, Colo. 80907. SECOND CONGRESS OF THE EUROPEAN ASSOCIATION OF

RADIOLOGY.

President, Professor Dr. J. R. von Ronnen, State University of Leiden, The Netherlands.

Voorhout, The Hague, The Netherlands. Congress Meeting: Amsterdam, The Netherlands, June 14-18,

FIRST ASIAN AND OCEANIAN CONGRESS OF RADIOLOGY Honorary Secretary, Dr. J. J. Martin, Box 805 F., G.P.O., Melbourne, 3001, Australia. Meeting: Melbourne, Australia, Nov. 22-26, 1971.

ALABAMA CHAPTER OF ACR

Secretary, Dr. William V. Weldon, Medical Arts Building, Birmingham, Ala. 35205. Meets time and place of Alabama State Medical Association.

ALASKA RADIOLOGICAL SOCIETY

Secretary, Dr. Bruce C. Wright, Providence Hospital, Anchorage, Alaska. Meets third Wednesday each month.

AMERICAN THERMOGRAPHIC SOCIETY

Secretary-Treasurer, Dr. Irwin M. Freundlich, Department of Radiology, Thomas Jefferson University Hospital, Philadelphia, Penn. 19107. Annual Meeting: Sheraton-Deauville Hotel, Atlantic City, N. J., June 20, 1971.
ARIZONA RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary, Dr. Wesley S. Fee, 2421 E. 6th St., Tucson, Ariz. 85719. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

ARKANSAS CHAPTER OF ACR
Secretary-Treasurer, Dr. Wilma C. Diner, Univ. of
Arkansas Medical Center, Little Rock, Ark. 72201. Meets twice annually, the Spring Meeting being in conjunction with and at the place of the State Medical Association.
Association of University Radiologists

Secretary-Treasurer, Dr. Elliott C. Lasser, University Hospital of San Diego County, San Diego, Calif. 92103. Annual Meeting: Durham, N. C., May 13-15, 1971, with the Duke University and University of North Carolina Radiology Departments serving, as co-hosts.

ATLANTA RADIOLOGICAL SOCIETY

Secretary, Dr. Richard S. Colvin, Emory University Clinic, Atlanta, Ga. 30322. Meets on four Thursday evenings during the academic year at a time announced in early September of each year, at the Academy of Medicine, Atlanta, Ga., at 8:00 p.m.
BAVARIAN-AMERICAN RADIOLOGIC SOCIETY

Advisor, Colonel Paul E. Sieber. Secretary, LTC Peter B. Riesz, USAH Bad Cannstatt, APO 09154, New York, N. Y. Meets quarterly.

BLOCKLEY RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. R. John Gould, 41 Lombardy Rd., Drexel Hill, Pa. 19026.

BLUEGRASS RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Eugene Slusher, Lexington Clinic, 1221 S. Broadway, Lexington, Ky. 40504. The Society meets once each month during the school year.

BRONX RADIOLOGICAL SOCIETY, NEW YORK STATE, CHAP-

Secretary-Treasurer, Dr. Leon J. Corbin, 1369 Rosedale Ave., Bronx, N. Y. 10472. Meets 4 times a year.

BROOKLYN RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Kenneth B. Robinson, 301 E. 75th St., Apt. 11-A, New York, N.Y. 10021. Meets first Thursday of each month, October through June.

<sup>\*</sup> Secretaries of societies are requested to send timely information promptly to the Editor.

BUFFALO RADIOLOGICAL SOCIETY

Secretary, Dr. Glen M. Ebersole, 405 Spring St., Jamestown, N.Y. 14701. Meets second Monday evening each month, October to May inclusive, at University Club.
California Radiological Society, California Chapter

of ACR

Secretary-Treasurer, Dr. John L. Gwinn, Childrens Hospital of Los Angeles, P.O. Box 54700, Los Angeles, Calif.

CATAWBA VALLEY RADIOLOGICAL SOCIETY

Secretary, Dr. Emmett R. White, P. O. Box 10, Rutherford College, N. C. 28671. Meets every Thursday, Dept. of Radiology. Valdese General Hosp., Valdese, N. C., at

CENTRAL NEW YORK RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. David N. Cheris, Community
General Hospital of Greater Syracuse, Broad Road, Syracuse, N. Y. 13215. Meets first Monday each month October through May.

CENTRAL OHIO RADIOLOGICAL SOCIETY

Secretary, Dr. James V. Blazek, 2,86 Lane Rd., Columbus, Ohio 4,3220. Meets second Thursday in October, November, January, and March 15, and May 19 at Fort Hayes Hotel, Columbus, Ohio.

CHICAGO ROENTGEN SOCIETY

Secretary-Treasurer, Dr. William T. Moss, 250 E. Superior St., Chicago, Ill. 60611. Meets third Thursday of each month, October to April, except December, at the Bismarck Hotel, Chicago, Ill.

CLEVELAND RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Daniel E. Wertman, 11311 Shaker Blvd., Cleveland, Ohio 44104. Meetings at 7:00 P.M. on fourth Monday of October, November, January,

February, March and April.
Colorado Radiological Society, Chapter of ACR Secretary, Dr. Marvin L. Daves, Univ. of Colorado Medical Center, 4200 E. Ninth Ave., Denver, Colo. 80220. Meets third Friday of each month at Denver Athletic Club from September through May.

Connecticut Valley Radiologic Society
Secretary, Dr. William W. Walthall, Jr., 130 Maple St.,
Springfield, Mass. Meets in April and October.

DALLAS-FORT WORTH RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Fred H. Dunn, 5940 Forest Park Rd., Suite 101, Dallas, Tex. 75235. Meets the 3rd Monday of every month at 6:30 P.M., at the Cibola Inn, Arlington, Tex.

DELAWARE CHAPTER OF ACE

Secretary, Dr. James H. Taylor, Wilmington Medical Center, Wilmington, Del. 19899.
EAST BAY RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. John C. Osmer, 20103 Lake Chabot Rd., Castro Valley, Calif. 94546. Meets first Thursday each month, Oct. through May, at University Club, Oakland, Calif.

EAST TENNESSEE RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Eberhard F. Besemann, Baroness Erlanger Hospital, Chattanooga, Tenn. 37403. Meets in January and September.

FLORIDA RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary, Dr. Wm. F. Lindsey, 1215 Hodges Dr., Tallahassee, Fla. 32303. Meets twice annually, in the spring with the annual State Society Meeting and in the fall.

FLORIDA WEST COAST RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Allen L. Sheer, University Community Hospital, 13505 N. 31st St., Tampa, Fla. 33612. Meets in January, March, May, July, September and November.

GEORGIA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Walker Harris, The Medical Center Columbus, Ga. 31902. Meets in spring and fall at Annual State Society Meeting.

GREATER CINCINNATI RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Owen L. Brown, 2421 Auburn Ave., Cincinnati, Ohio 45219.

GREATER LOUISVILLE RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. L. D. LeNeave, 315 E. Broad-

way, Louisville, Ky. 40202. Meets monthly.

GREATER MIAMI RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. John Kathe, North Shore Hospital, Miami, Fla. 33150. Meets monthly, third Wednesday at 8:00 P.M. at various member hospitals, Miami, Fla. GREATER ST. LOUIS SOCIETY OF RADIOLOGISTS

Secretary-Treasurer, Dr. Roland P. Ernst, 3720 Washington Ave., St. Louis, Mo. 63108.

HAWAII RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Ghim L. Yeoh, Prof. Center Bldg., 1481 S. King St., Honolulu, Hawaii 96814. Meets third Monday of each month at 7:30 P.M.

HEALTH PHYSICS SOCIETY

Secretary John H. Pingel, Argonne National Laboratory, 9700 S. Cass Ave., Argonne, Ill. 60439, Annual Meeting: Waldorf Astoria Hotel, New York City, July 11-15, 1971.

HOUSTON RADIOLOGICAL SOCIETY

Secretary, Dr. Kenneth M. Jensen, 1615 St. Joseph Prof. Bldg., Houston, Texas 77002. Meets fourth Monday of each month, except June, July, August and December, at 6:00 P.M., at 103 Jesse H. Jones Library Building, Texas Medical Center, Houston, Tex. 77025

IDAHO STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Hugh P. Smith, Jr., 130 E. Bannock, Boise, Id. 83702. Meets in the spring and fall.

ILLINOIS RADIOLOGICAL SOCIETY, INC., CHAPTER OF ACR

Secretary, Dr. Jack L. Melamed, 1230 Sunset Rd. Winnetka, Ill. 60093. Meets in the spring and fall. Indiana Roentgen Society, Inc., Chapter of ACR Secretary, Dr. Dale B. Parshall, Elkhart General Hospital, P.O. Box 1329, Elkhart, Ind. 46514.

Iowa Radiological Society, Chapter of ACR Secretary-Treasurer, Dr. John Huston Jr., 1948 First Ave. N.E., Cedar Rapids, Iowa 52402. Luncheon and business meeting during annual session of Iowa State business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

KANSAS RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Wm. R. Allen, 155 S. 18th St. Kansas City, Kan. 66102. Meets in spring with State Medical Society and in winter on call.

KENTUCKY CHAPTER OF ACR

Secretary-Treasurer, Dr. Joan R. Hale, 402 Heyburn Bldg. Louisville, Ky. 40202. Meets in April and September.

KINGS COUNTY RADIOLOGICAL SOCIETY

Secretary, Dr. Sidney Hendler, 1880 Ocean Ave., Brooklyn 30, N.Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

KNOXVILLE RADIOLOGICAL SOCIETY Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

LONG ISLAND RADIOLOGICAL SOCIETY

Secretary, Dr. Harold L. Atkins, 1200 Stewart Ave., Garden City, N. Y. 11533. Meets monthly.

Los Angeles Radiological Society

Secretary, Dr. Harry T. Vanley, St. Mary's Long Beach Hospital, Long Beach, Calif. 90083. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles, Calif.

LOUISIANA-TEXAS GULF COAST RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Edward A. Sheldon, 109 Doctors

Bldg., Beaumont, Tex. 77701

Maine Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Richard W. Taylor, Radiology Department, St. Mary's General Hospital, Lewiston, Maine 04240. Meets in June, September, December and April. MARYLAND RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary, Dr. Nathan Stofberg, 4519 Hawksbury Rd., Pikesville, Md. 21208.

MASSACHUSETTS RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Norman L. Siadowsky, The Faulkner Hosp., 1153 Centre St., Jamaica Plain, Mass. 02130 Memphis Roentgen Society

Secretary-Treasurer, Dr. Webster Riggs, Jr., The University of Tennessee College of Medicine, Department of Radiology, Walter F. Chandler Bldg.. 865 Jefferson Ave., Memphis, Tenn. 38103. Meets first Monday of each month at John Gaston Hospital.

MIAMI VALLEY RADIOLOGICAL SOCIETY

Secretary, Dr. Darwood B. Hance, Reid Memorial Hospital, Richmond, Ind. Meets third Thursday of fall. winter and spring months at 7:30 P.M. at Miami Valley Hospital, Dayton, Ohio.

MICHIGAN RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. David P. Corbett, Harper Hospital, Detroit, Mich. 48201. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6: 30 P.M.

MID-HUDSON RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Herbert S. Berlin, Hopewell Junction, N. Y. Meets 7:00 P.M., first Wednesday of each month, September to May.

MILWAUKEE ROENTGEN RAY SOCIETY

Secretary-Treasurer, Dr. James E. Bell, 8700 W. Wisconsin Ave., Milwaukee, Wis. 53213. Meets monthly on fourth Monday, October through May, at University Club.

MINNESOTA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Warren L. Kump, 4243 Glenwood Ave., Minneapolis, Minn. 55422. Meets twice annually, fall and winter.

MISSISSIPPI STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary-Treasurer, Dr. Ottis G. Ball, 5356 Balmoral Drive, Jackson, Miss. 39211. Meets third Thursday of each month at the Heidelberg Hotel, Jackson, at 6:00 P.M.

MISSOURI RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Arthur A. Porporis, 100 N. Euclid Ave., St. Louis, Mo. 63108.

MONTANA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Jon A. Anderson, Doctor's Building, 1231 N. 29th Street, Billings, Mont. 59101.

NEBRASKA CHAPTER OF ACR

Secretary-Treasurer, Dr. N. Patrick Kenney, 3618 S. 114th Ave., Omaha, Nebr. 68144. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

NEVADA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Harris W. Knudson, 2020 W. Charleston Blvd., Las Vegas, Nev. 89102.

NEW ENGLAND ROENTGEN RAY SOCIETY

Secretary, Dr. Stefan C. Schatzki, 1180 Beacon St., Brookline Mass. 02146. Meets third Friday of each month, October through April, excluding December, at The Longwood Towers, 20 Chapel Street, Brookline, Mass., at 4:30 P.M. New Hampshire Roentgen Ray Society, Chapter of

Secretary, George Farmlett, 33 Round Bay Rd., Keene, N. H. 03246. Meets four to six times yearly.

New Mexico Society of Radiologists Chapter of ACR Secretary, Dr. Donald A. Wolfel, Albuquerque, New Mexico. Four meetings annually, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

New York Roentgen Society Secretary-Treasurer, Dr. Samuel H. Madell, 1. E. 82nd St., New York, N. Y. 10028. Meets monthly on third Monday at the New York Academy of Medicine at 4:30 P.M. Annual Spring Conference: Waldorf Astoria Hotel, New York, April 29-May 1, 1971. Further information may be obtained from Dr. Albert A. Dunn, Roosevelt Hosp.,

New York, N. Y. 10019. New York State Chapter of ACR

Secretary-Treasurer, Dr. John J. Magovern, 520 Frank-lin Ave., Garden City, N. Y. 11530.

NORTH CAROLINA CHAPTER OF ACR.

Secretary-Treasurer, Dr. James F. Martin, 300 S. Hawthorne Road, Winston-Salem, N. C. 27103.

NORTH DAKOTA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Marshall Landa, 1702 13th St., So.,

Fargo, N. D. 58102. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

NORTH FLORIDA RADIOLOGICAL SOCIETY

Secretary, Dr. John W. Morris, III., Department of Radiology, Halifax District Hospital, Daytona Beach, Fla. 32015. Meets quarterly in March, June, September and December.

NORTHEASTERN NEW YORK RADIOLOGICAL SOCIETY

Secretary, Dr. Barbara Chick, Glens Falls Hospital, Glens Falls, N.Y. 12801. Meets in Albany area on third Wednesday of October, November, March, April, and

NORTHERN CALIFORNIA RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Kevin Ryan, Woodland Medical group, Woodland, Calif. 95695. Meets fourth Monday of Sept., Nov., Jan., March and May at Aldo's Restaurant in Sacramento.

NORTHWESTERN OHIO RADIOLOGICAL SOCIETY

Secretary, Dr. Vito J. Zupa, Mercy Hospital, Department of Radiology, Toledo, Ohio.

Ohio State Radiological Society, Chapter of ACR

Secretary, Dr. Joseph Hanson, 1544 South Byrne Road. Toledo, Óhio 43614.

OKLAHOMA STATE RADIOLOGICAL SOCIETY, CHAPTER OF

Secretary, Dr. Richard B. Price, 204 Medical Tower Bldg., Oklahoma City, Okla. 73112. Meets in January, May and October.

ORANGE COUNTY RADIOLOGICAL SOCIETY

Secretary, Dr. Edward I. Miller, 301 Newport Blvd., Newport Beach, Calif. 92660. Meets on fourth Tuesday of the month, excluding June, July, August, and December, at the Orange County Medical Association Bldg.. Orange, Calif.

OREGON STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. Gerlad L. Warnock, 11699 N. E. Glisan St., Portland, Ore. 97220. Meets on second Wednesday of month, October through April, at the University Club, Portland, Ore.

ORLEANS PARISH RADIOLOGICAL SOCIETY

Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans, La. 70113. Meets second Tuesday of each

Pacific Northwest Radiological Society

Secretary-Treasurer, Dr. Robert S. Miller, 13753 S.W. Farmington Rd.; Beaverton, Oregon 97005. Meets annually in Portland, Oregon, Seattle, Washington or Victoria or Vancouver, British Columbia, in early May.

Pennsylvania Radiological Society, Chapter of ACR Secretary, Dr. Theodore A. Tristan, Harrisburg Polyclinic Hosp., Harrisburg, Pa. 17105.

PHILADELPHIA ROENTGEN RAY SOCIETY

Secretary, Dr. C. Jules Rominger, Misericordia Hospital, 54th St. and Cedar Ave., Philadelphia, Pa. 19143. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

PITTSBURGH ROENTGEN SOCIETY

Secretary, Dr. Stephen C. Bruno, Shadyside Hospital, 5230 Centre Ave., Pittsburgh, Pa. 15232. Meets second Wednesday of month, October through June, at Park Schenley Restaurant.

RADIATION RESEARCH SOCIETY

Executive Secretary, Richard J. Burk, Jr., 4211 39th St., N.W., Washington, D. C. 20016. Annual Meeting: Boston, Mass., May 9-13, 1971.

RADIOLOGICAL SOCIETY OF CONNECTICUT, INC., CHAPTER

Secretary-Treasurer, Dr. Carl W. Scheer, 335 Cook Ave., Meriden, Conn. 06450. Meetings are held quarterly

RADIOLOGICAL SOCIETY OF GREATER CINCINNATI Secretary Treasurer, Dr. Donald E. Gunderson, 3553 Bayard Dr., Cincinnati, Ohio 45208. Meets first Monday of each month at Cincinnati Academy of Medicine.

RADIOLOGICAL SOCIETY OF GREATER KANSAS CITY Secretary, Dr. Ken C. Davidson, St. Luke's Hospital of Kansas City, Kansas City, Mo. 84111. Meets 5 times a year on given dates.

RADIOLOGICAL SOCIETY OF KANSAS CITY

Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

RADIOLOGICAL SOCIETY OF LOUISIANA, CHAPTER OF ACR Secretary, Dr. Ralph B. Bergerson, 154 Brockenbraugh Ct. Metairie, La. 70005. Meets semiannually during Louisiana State Medical Society meeting and 6 months

RADIOLOGICAL SOCIETY OF NEW JERSEY, CHAPTER OF ACR Secretary, Dr. Sidney Ketyer, St. Elizabeth Hosp., 225 Williamson St., Elizabeth, N. J. 07206. Meets in Atlantic City at time of State Medical Society meeting and in

October or November in Newark, N. J.

RADIOLOGICAL SOCIETY OF RHODE ISLAND, CHAPTER OF

Secretary-Treasurer, Dr. John J. O'Brien, 292 Merrymount Dr., Warwick, R.I. 02888.

RADIOLOGICAL SOCIETY OF SOUTHERN CALIFORNIA Secretary-Treasurer, Dr. Gladden V. Elliott, 5565 Gross-mont Center Dr., Suite 1, La Mesa, Calif. 92041. Meets three times a year, usually October, February and May.

RADIOLOGICAL SOCIETY OF THE STATE OF NEW YORK

Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood
Ave., Rochester, N. Y. 14618.

REDWOOD EMPIRE RADIOLOGICAL SOCIETY

Secretary, Dr. Lee F. Titus, 164 W. Napa St., Sonoma. Calif. Meets second Monday every other month.

RICHMOND COUNTY RADIOLOGICAL SOCIETY Secretary, Dr. M. Pinson Neal, Jr., Medical College of Virginia, 1200 E. Broad St., Richmond, Va. 23219. Meets first Thursday of each month at various hospitals.

ROCHESTER ROENTGEN RAY SOCIETY, ROCHESTER, N. Y. Secretary, Dr. Kenneth E. Robinson, Rochester General Hospital, 1425 Portland Ave., Rochester, N. Y. 14621. Quarterly meetings on the call of the President, at the Rochester Academy of Medicine.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Lorenz R. Wurtzebach, 4200 E. Ninth Ave., Denver. Colo. 80220. Annual meeting: Brown Palace Hotel, Denver, Colo., Aug. 19-21, 1971.

SAN ANTONIO-CIVILIAN-MILITARY RADIOLOGICAL SOCIETY AN ANTONIO-IVITIAN-INITIATY NADIOUGIAL SOCIETY Secretary, Dr. Lee F. Rogers, Department of Radiother-apy, Bexar County Teaching Hospital, 4502 Medical Drive, San Antonio, Texas. Meets third Wednesday of each month at Fort Sam Houston Officers' Club at 6:30

SAN DIEGO RADIOLOGICAL SOCIETY

President-Secretary, Dr. James M. Lee, Scripps Clinic and Research Found., 476 Prospect St., La Jolla, Calif. 92037. Meets first Wednesday of each month at the Town & Country Hotel.

San Francisco Radfological Society

Secretary-Treasurer, Dr. James G. Moore, 20 Bridge Rd., Kentfield, Calif. 94904. Meets quarterly at various hospitals (contact Secretary).

SANTA CLARA COUNTY RADIOLOGICAL SOCIETY

Secretary, Dr. Raymond L. Schwinn, 480 Monterey Ave., Los Gatos, Calif. 95030. Meets monthly at the Santa Clara County Medical Association Bldg., 700 Empey Way, San Jose, Calif.

Section on Radiology, California Medical Association Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Medical Society of the Dis-TRICT OF COLUMBIA

Secretary-Treasurer, Dr. Louis Wener, Cafritz Memorial Hosp., 1310 Southern Ave., S.E., Washington, D. C. 20032. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Southern Medical Association Secretary, Dr. Phillip W. Voltz, Jr., 120 Medical Professional Bldg., San Antonio, Tex. 78212.

Section on Radiology, Texas Medical Association Secretary, Dr. George F. Crawford, St. Elizabeth Hospi-

tal, Beaumont, Tex. Meets annually with the Texas Medical Association.

SHREVEPORT RADIOLOGICAL CLUB

Secretary, Dr. W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday at 7:30 P.M., September to May inclusive.

SOCIETY FOR PEDIATRIC RADIOLOGY

Secretary, Dr. John L. Gwinn, Children's Hospital, 4614 Sunset Blvd., Los Angeles 27, Calif. Annual meeting: Sheraton Hotel, Boston, Mass., September 26–27, 1971.

SOCIETY OF NUCLEAR MEDICINE Secretary, Dr. James J. Smith, 140 E. 54th St., New York, N. Y. Administrative Officer, Mrs. Margaret Glos, 211 E. 43rd St., New York, N. Y. 10017. Annual meet-

ing: Los Angeles, Calif., June 26-July 2, 1971.
South Bay Radiological Society
Secretary, Dr. Emerson C. Curtis, University Dr., Menlo Park, Calif. 94025. Meets second Wednesday of each month.

South Carolina Radiological Society, Chapter of ACR Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Associa-tion meeting in May. Annual fall scientific meeting at time and place designated by the president.

South Dakota Radiological Society, Chapter of ACR Secretary, Dr. Haakon O. Haugan, 716 Quincy St., Rapid City, S. D. 57701. Meets in spring with State Medical

Society and in fall.

Southern California Radiation Therapy Society Secretary-Treasurer, Dr. Aaron G. Fingerhut, 1000 W. Carson St., Torrance, Calif. 90502. Meets quarterly.

SOUTHERN RADIOLOGICAL CONFERENCE

Secretary-Treasurer, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 7544, Mobile, Ala. 36607. Sixteenth Annual Meeting: Grand Hotel, Point Clear, Ala., Jan. 28-30, 1972.

SOUTHWESTERN RADIOLOGICAL SOCIETY Secretary, John M. McGuire, 904 Chelsea, El Paso.

Tex. Meets last Monday of each month at 6:30 P.M. in

the Paso del Norte Hotel.

Tennessee Radiological Society, Chapter of ACR Secretary-Treasurer, Dr. Lawrence R. Nickell, Maury County Hospital, Columbia, Tenn. 38401. Meets annually at the time and place of the Tennessee State Medical Association meeting.

TEXAS STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. Herman C. Sehested, 815 Medical Tower, Room 100, 1550 W. Rosedale St., Fort Worth, Tex. 76104. Annual meeting at the Flagship Hotel on Pier, Galveston, Tex.

THE FLEICHNER SOCIETY

Secretary-Treasurer, Eric N. C. Milne, M.B., Medical Sciences Bldg., University of Toronto, Ontario, Canada. Meets in Williamsburg, Va., at the Williamsburg Conference Center, in conjunction with a course on "Modern Trends in Roentgenology of the Chest," sponsored by the Virginia Commonwealth University, Richmond, Va., March 14-18, 1971. Tri-State Radiological Society

Secretary, Dr. John H. Marchand, Jr., Methodist Hospital, Henderson, Ky. Meets third Wednesday of Oct., Jan., March and May, 8:00 P.M., Elks Club in Evansville, Ind.

University of Michigan Department of Roentgen-OLOGY STAFF MEETING

Meets each Monday evening from September to June, at 7:∞ P.M. at University Hospital, Ann Arbor, Mich.

UPPER PENINSULA RADIOLOGICAL SOCIETY

Secretary, Dr. A. Gonty, Menominee, Mich. Meets

UTAH STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. R. Newell Ford, St. Mark Hospital, 803 North 2nd West, Salt Lake City, Utah 84103. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital. VERMONT RADIOLOGICAL SOCIETY, CHAPTER OF ACR

Secretary, Dr. Edward A. Kupic, Mary Fletcher Hosp., Burlington, Vt. 05401.

VIRGINIA CHAPTER OF ACR

Secretary-Treasurer, Dr. James S. Redmond, Suite 7,

Medical Center, Lynchburg, Va. 24501.
Washington, D. C., Chapter of ACR
Secretary-Treasurer, Dr. Joan Wohlgemuth, 5021 Seminary Rd., Alexandria, Va. 22311.

WASHINGTON STATE RADIOLOGICAL SOCIETY, CHAPTER OF

Secretary-Treasurer, Dr. Paul S. Paulson, 1001 Broadway Seattle, Washington 98122. Meets quarterly.

WEST VIRGINIA RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary-Treasurer, Dr. J. Dennis Kugel, 510-517 Med. Arts Bldg. Charleston, W. Va. 25301. Meets concurrently with annual meeting of West Virginia State Medical Society; other meetings arranged by program committee. Westchester County Radiological Society

Secretary, Dr. Edgar Palmer, 650 Main St., New Rochelle, N. Y. 10801. Meets on third Tuesday of January

and October and on two other dates.

Wisconsin Radiological Society, Chapter of ACR Secretary-Treasurer, Dr. Robert E. Douglas, 1209 S. Commercial St., Neenah, Wis. 54956. Meets twice a year, May and September.

WYOMING RADIOLOGICAL SOCIETY, CHAPTER OF ACR Secretary, Dr. J. D. Grant, Memorial Hosp., Sheridan, Wyo. Meets in fall with State Medical Society and in spring on call of President.

#### MEXICO, PUERTO RICO AND CENTRAL AMERICA

Asociación Costarricense de Radiología

Secretary, Dr. Jorge Vargas Segura, Apartado 5367, San José, Costa Rica.

San Jose, Costa Rica.

Asociación de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.

Secretary-General, Dr. Roberto Calderón, Calle Central

Oeste No. 218, Managua, Nicaragua, Central America. Meets annually in a rotating manner in the six countries. Asociación Puertorriqueña de Radiología

Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico

SOCIEDAD DE RADIOLOGÍA DE EL SALVADOR

Secretary, Dr. Julio Astacio, 5a Av. Nte. No. 434, San Salvador, Rep. El Salvador.

Sociedad de Radiología de Guatemala Secretary, Dr. Carlos E. Escobar, 92. Calle A 0-05, Zona 1, Guatemala.

Sociedad Mexicana de Radiología, A.C.

Coahuila No. 35, México 7, D.F. Secretary-General, Dr. Octavio Toussaint Goribar. Meets first Monday of each month.

Sociedad Radiológica Panameña

Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting. Sociedad Radiológica de Puerto Rico

Secretary, Dr. Heriberto Pagán Sáez, Box 9387, Santurce, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

#### BRITISH COMMONWEALTH OF NATIONS

Association of Radiologists of the Province of Que-

Secretary, Dr. Pierre Archambault, Hôpital Charle Le Moyne, 121 Boul. Taschereau, Greenfield Park, P.Q., Canada. Meets four times a year.

BRITISH INSTITUTE OF RADIOLOGY

Honorary Secretary, Dr. G. H. du Boulay, 32 Welbeck St., London, W. 1, England. Meets monthly from October until May.

CANADIAN ASSOCIATION OF PHYSICISTS, DIVISION OF MEDICAL AND BIOLOGICAL PHYSICS.

Honorary Secretary Treasurer, Dr. R. G. Baker, Ontario

Cancer Foundation, Ottawa Civic Clinic, 1053 Carling

Ave., Ottawa 3, Ont., Canada.
Edmonton and District Radiological Society

Secretary, Dr. L. A. Koller, Suite 360, Professional Bldg., 10830 Jasper Ave., Edmonton 15, Alberta, Canada Meets third Thursday of each month October to May, except December, at various Edmonton Hospitals.

FACULTY OF RADIOLOGISTS Honorary Secretary, Robert Morrison, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting, Oxford, England, July 2-3, 1971.

FACULTY OF RADIOLOGISTS, ROYAL COLLEGE OF SURGEONS

IN TRELAND Registrar, Dr. H. O'Flanagan, F.R.C.P.I., D.P.H., 123

St. Stephens Green, Dublin 2, Ireland. SECTION OF RADIOLOGY OF THE ROYAL SOCIETY OF MEDI-

CINE (CONFINED TO MEDICAL MEMBERS) Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1, En-

CANADIAN ASSOCIATION OF RADIOLOGISTS

Honorary Secretary, Dr. F. Robert MacDonald, Associate Honorary Secretary, Dr. Champlain Charest, 1555 Summerhill Ave., Montreal 25, Que., Canada. Annual meeting: Palliser Hotel, Calgary, Alberta, March 15-19, 1971.

MONTREAL RADIOLOGICAL STUDY CLUB Secretary, Dr. W. Paul Butt, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening,

October to April.

Section of Radiology, Canadian Medical Association Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française de Radiologie Secretary General, Dr. Guy Duckett, 1385 est, rue Jean Talon, Montréal, P.Q., Canada. Meets every third Tuesday from October to April.

TORONTO RADIOLOGICAL SOCIETY

Secretary, Dr. George Wortzman, Toronto General Hosp. Toronto 12, Ont., Canada. Meets second Monday of each month, September, through May.

COLLEGE OF RADIOLOGISTS OF AUSTRALASIA Honorary Secretary, Dr. T. P. Loneragan, 147 Macquarie St., Sydney, N.S.W., Australia.

#### South America

Asociación Argentina de Radiología

Secretary, Dr. Lidio G. Mosca, Avda. Fral. Paz 151, Córdoba, Argentina. Meetings held monthly.

Ateneo de Radiologia

Secretary, Dr. Víctor A. Añaños, Instituto de Radiologia, Urqiza 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 P.M. in the Hospital Nacional de Centenario, Santa Fe 1300, Rosario. Colégio Brasileiro de Radiologia

Secretary-General, Dr. Miguel Mario Céntola, Caixa Postal 5984, São Paulo, Brazil.

Sociedad Argentina de Radiología

Secretary-General, Dr. Juan R. Heilbuth Pacheco, Santa Fe 1171, Buenos Aires. Meets first Wednesday evening, April through December.

Sociedad Boliviana de Radiología Secretary, Dr. Javier Prada Méndez, Casilla 1182, La Paz, Bolivia. Meets monthly. General assembly once

every two years.

Sociedade Brasileira de Radiologia Secretary, Dr. Armando Rocha Amoédo, Cxa Postal 1532, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia

Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigaderio Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

ociedad Chilena de Radiología

Secretary, Dr. Ricardo Cortez, Casilla, 13426 Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia

Secretary-General, Dr. Raúl Fernández Angula, Calle 43 No. 44-70 Barranquilla, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología

Secretary, Dr. Carlos Palau Jimenez, Casilla 4569, Guayaquil. Ecuador.

Sociedad Paraguaya de Radiología

Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay,

Sociedad Peruana de Radiologia

Secretary-General, Dr. Julio Ormeño del Pino, Instituto de Radiología "Cayetano Heredia" Hospital Arzobispo Loayza, Lima, Perú. Meets monthly except during January, February, and March.

Sociedad de Radiologia del Atlantico

Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiología.

Sociedad de Radiología del Nordeste Argentino Secretary-General, Dr. Francisco I. Velar, Catamarca 561, Corrientes, Argentina.

Sociedad de Radiología de la Plata

Secretary. Dr. Hiram D. Haurigot, Calle 50 No. 374, La Plata, Argentina.

Sociedad de Radiología, Cancerología y Física MÉDICA DEL URUGUAY

Secretary-General, Dr. Miguel A. Sica, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.
Sociedade de Radiología de Pernambuco

Secretary, Dr. Manoel Medeiros Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife.

Caixa Postal 505, Pernambuco, Brazil.
Sociedad de Roentgenología y Medicina Nuclear de la Provincia de Córdoba

Secretary-General, Dr. Lucas C. Di Rienzo, Ave. Grl.

Paz. 151, Córdoba, Argentina. Sociedad Salteña de Radiología y Medicina Nuclear Secretary, Dr. Mario A. Moya, Av. Sarmiento 536, Salta, Argentina.

Sociedad Venezolana de Radiología y Medicina Nu-CLEAR

Secretary-General, Dr. Modesto Rivero Gonzáles, Apartado Postal 9213, Candelaria, Caracas, Venezuela. Meets monthly, third Friday at Colegio Médico del Distrito Federal, Caracas.

#### CONTINENTAL EUROPE

ÖSTERREICHISCHE RONTGEN-GESELLSCHAFT

President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

Société Royale Belge de Radiologie

General Secretary, Dr. Joseph Baeyens, Alost, Belgium. Meets in February, March, May, June, September, October, November and December.

Société Européenne de Radiologie Pédiatrique President, Dr. George Thomsen, Rigshospitalet (University Hospital), Blegdamsvej 9, DK 2100 Copenhagen, Denmark. Meets in Elseneur, Denmark, May 12-15, 1971.

Permanent Secretary, Clément Fauré, Hôpital des Enfants-Malades, 149, rue de Sèvres, Paris 15e, France.

Société Française d'Electroradiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral MÉDITERRANÉEN, DU CENTRE ET DU LYONNAIS, DU NORD, DE L'OUEST, DE L'EST, ET D'ALGER ET D'AFRIQUE DU NORD. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France.

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South Africa.



# ABSTRACTS OF RADIOLOGICAL LITERATURE

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#### ROENTGEN DIAGNOSIS

#### NECK AND CHEST

AMELUNG, D. Alcoholic cardiomyopathy. German Med. Monthly, Sept., 1970, 15, 515-520. (Address: Medizinische Klinik des Diakonissenhauses Elisabethenstift, Landgraf-Georg-Strasse 100, 61, Darmstadt, Germany.)

The author reports 3 men who had consumed large amounts of alcohol, mainly in the form of beer, for many years. These men developed marked cardiomegaly with right and left heart failure and massive edema. The clinical picture of alcoholic cardiomyopathy has a favorable prognosis if it is recognized early and the abuse of alcohol stopped. The possibility of alcoholic cardiomyopathy must be excluded, particularly in younger patients with heart disease of uncertain etiology. The picture of the beri-beri heart with predominantly right-sided cardiac failure and an increased cardiac output is seen much more rarely in the chronic alcoholic. It responds to vitamin B<sub>1</sub>, whereas alcoholic cardiomyopathy responds to abstinence from alcohol, together with the usual therapeutic measures for cardiac failure (bed rest. salt-restricted diet, digitalis), usually with rapid reversal of cardiac failure, especially in the early stages.

The author also calls attention to the consumption of cobalt-containing beer which was first observed in the U. S. A. and Canada, and later in Belgium. Of 28 cases seen in Quebec in 1965, 20 died, 14 of the deaths occurring within 24 hours of admission to the hospital. In Omaha 30 out of 64 patients died. Intensive investigations to explain the remarkably high accumulation of cardiac deaths within a few months revealed that the disease was due to cobalt which had been added to the beer as a froth-stabilizer. The first cases of poisoning were seen 1 month after the introduction of the cobalt additive, and no further new cases occurred I month after the addition of cobalt had been stopped. The concentration of cobalt in the heart muscle tissue of patients who died was about 10 times normal. In the cases observed in Belgium the course was less severe: only 1 of 24 patients died. It is possible that the more favorable course in Belgium was related to the higher protein intake of the patients; the Canadian patients had a relatively low protein intake.

One remarkable feature in this special form of alcoholic cardiomyopathy was that the cobalt exerted its toxic effect only in conjunction with beer. Administration of cobalt alone, even in higher doses, had not hitherto been found to have any cardiotoxic effect. It was, therefore, suspected that alcohol rendered the heart muscle especially sensitive to the toxic effect of cobalt.—C. Peter Truog, M.D.

Serres, J. J., Pène, P., Bourgeade, A., and Lesquerré, C. Étude radiologique du pneumomédiastin spontané chez l'enfant rougeoleux en milieu tropical. (Radiologic study of spontaneous pneumomediastinum in the child suffering from measles in the Tropics.) J. de radiol., d'électrol. et de méd. nucléaire, June-July, 1970, 51, 369-372. (From: Service d'Electroradiologie et Service des Maladies Infectieuses, C.H.U. d'Abidjan, Côted'Ivoire, Africa.)

The report is based on 46 cases of spontaneous pneumomediastinum from a group of 3,000 children living in the Tropics and hospitalized for measles. The main diseases causing spontaneous pneumomediastinum are: pulmonary tuberculosis, and acute and chronic pulmonary diseases, among which whooping cough and measles are frequently the responsible infections.

The current explanation for the presence of air in the mediastinum is an alveolar rupture resulting from a disturbed airflow, or from coughing. The escaped air reaches the mediastinum via the perivascular tissue. An increased fragility of the alveolar wall due to the infectious process must be considered as an added reason for the greater occurrence of this complication in measles.

The male children were the more frequently affected: 38 out of a total of 46 cases. Most of the cases (91 per cent) were under 3 years of age and poorly nourished. This complication occurred during the first days of the rash in 30 per cent of cases. In the others, it appeared during the desquamation phase. The highest incidence was found between the months of January and May, this being the warmest period of the year.

The diagnosis was established clinically in 31 cases by the presence of subcutaneous emphysema above the sternum, and roentgenologically in 13 cases. Two cases were recognized at autopsy.

Clinically, the cervicomediastinal emphysema appeared insidiously. However, 6 cases died on the very day of the detection of subcutaneous emphysema, although such a fatal outcome had not been expected from the clinical standpoint.

Roentgenologic study. This study is important in order to establish the pneumomediastinum even when subcutaneous emphysema is clinically evident. The chest roentgenograms were taken in decubitus for greater facility. In decreasing order of frequency, the findings on the anteroposterior roentgenograms were as follows: uni- or bilateral mediastinal radio-lucent bands; a fine air crescent surrounding the aortic knob (in 5 cases, it was the only roentgenologic localization); fasciculation of the main vessels of the cardiac base by peripheral contrast air; a line or band of air along the left lateral border of the descending aorta, which is prolonged under the diaphragm and creates a retropneumoperitoneum; and a small collection of air at the cardiac apex.

In 11 cases, lateral roentgenograms were also ob-

tained. In all these cases the retrosternal radiolucent triangle (spinnaker sail) and the increased triangular radiolucency in the lower retrocardiac area were demonstrated.

The lung fields showed the usual changes observed in measles: prominent hili and increased bronchovascular markings in the bases. In 16 cases, bilateral opaque nodules or bronchopneumonic infiltrates were observed. In 12 cases, diffuse emphysema was associated and 2 cases showed bullous emphysema. Only I case showed a pleural effusion 8 days after the pneumomediastinum. Pneumothorax was observed in 3 cases.

In the favorable cases (27 out of 46) the subcutaneous emphysema was absorbed in 4 to 15 days. The pneumomediastinum disappeared in 8 to 12 days.—H. P. Lévesque, M.D.

Quaglia, C., Arena, G. C., Ragni, G., and Zanini, E. Studio chimografico della dinamica dell'arco aortico e della valvola artificiale dopo intervento di valvuloprotesi aortica: criteri di valutazione dei risultati postoperatori. (Kymographic study of the dynamics of the aortic arch and of the artificial valve after intervention for aortic valvuloprosthesis: criteria of evaluation of the postoperative results.) Radiol. med., April, 1970, 56, 289–306. (Address: Dott. Prof. Carlo Quaglia, Istituto di Radiologia dell'Università, Via Genova, 3, Torino, Italy.)

For the past few years the authors have studied by analytic roentgen kymography the pulsations of the thoracic aorta in 5 patients, who were operated on because of aortic insufficiency and in whom an artificial valve had been inserted.

The high degree of opacity of the valve has permitted its accurate localization in one or more analytic slits, to determine the type of movements of the valve, and to compare them with the pulsations of the left ventricle and of the proximal segment of the ascending aorta.

All the kymographic studies were performed after a minimum of 6 months following surgery. The examination was carried out in the posteroanterior and left anterior oblique projections.

Analyzed in detail were the 3 factors which influence the movements of the aorta: (1) the aortic pulsations; (2) the aortic flow; and (3) the movements of the ascending aorta and their relationship with the ventricular contractility.

The conclusions which were reached can be summarized as follows: (1) the morphology of the roent-gen kymographic waves of the aortic knob mirrors with fidelity the normalization of the hemodynamic conditions of the vessels after a satisfactory valvular replacement; (2) the presence of a valvuloprosthesis

does not affect in any way the analytic kymographic tracings either of the aorta or of the left ventricle; (3) the tracings obtained in the 2 projections demonstrate quite clearly that (a) there is a downward movement of the valve toward the apex of the heart, which does not always occur at the moment of the ventricular contraction and (b) that the same valvular movements result from the pendular, or better, oscillatory movements of the valve itself in the aortic lumen.

Several reproductions of the analytic kymograms obtained in the 5 cases illustrate the article.—A. F. Govoni, M.D.

KIRSH, MARVIN M., CRANE, JAMES D., KAHN, DONALD R., GAGO, OTTO, MOORES, WILLIAM Y., REDMAN, HELEN, BOOKSTEIN, JOSEPH H., and SLOAN, HERBERT. Roent-genographic evaluation of traumatic rupture of the aorta. Surg., Gynec. & Obst., Nov., 1970, 131, 900–904. (From: Departments of Surgery and Radiology, University of Michigan Medical Center, Ann Arbor, Mich.)

The authors state that during the past 4 years, they have seen 14 patients with acute rupture of the thoracic aorta. During the same period, an additional 13 patients with closed chest trauma had aortography performed because aortic rupture was suspected. The findings on the plain roentgenograms of the chest of these 2 groups of patients have been compared to determine if the diagnosis of ruptured aorta can be firmly established on the basis of plain film roentgenographic findings alone.

In Group 1, they consider 14 patients in whom a traumatic rupture of the aorta was sustained in traffic accidents. Eight of these patients presented external evidence of thoracic injury or rib fractures; 6 had upper extremity hypertension; and in 5 patients a harsh systolic murmur was audible over the precordium or interscapular region. Associated injuries, such as fractures of the extremities, head injuries, splenic lacerations, and lacerations of small or large intestinal mesentery, occurred separately or together in all these patients. Twelve of the 14 patients underwent operation within 48 hours of injury, and II survived. One patient underwent repair of the aortic rupture 6 days after injury and survived. One patient died from exsanguination on admission, before an aortogram could be obtained; at autopsy, this patient had two aortic lacerations, one just above the diaphragm and the other just distal to the ligamentum arteriosum.

Aortography confirmed the diagnosis in 13 of the patients in *Group 1*. Aortography was performed by the retrograde femoral approach in 10 and by the axillary approach in 2 patients. In 1 patient, aortography was performed by the intravenous administration of contrast emedium. All 13 patients had pseudoaneurysm formation at or near the ligamen-

tum arteriosum. The appearance was unmistakable and characteristic in each patient. The tear itself was not always clearly defined, but the sac of the false aneurysm or a radiolucent line formed by the retracted intima and media was seen in all patients.

In Group 11, 12 of the 13 patients sustained blunt trauma to the chest in automobile accidents, and 1 patient was injured when he fell from a silo. External evidence of thoracic injury or rib fractures was present in 10 patients; 7 patients had upper extremity hypertension; and in 1 patient a harsh systolic murmur, audible over the precordium or in the interscapular region, was noted.

Aortography was performed by retrograde femoral approach in all 13 patients of this group.

In summarizing, the authors state that diagnosis of traumatic rupture of the aorta should be considered in all victims of severe deceleration accidents whether or not there is external evidence of thoracic injury. The diagnosis should be further suspected if superior mediastinal widening, abnormal or obliterated aortic contours, depression of the left main stem bronchus, or deviation of the trachea to the right are present on plain roentgenograms of the chest. However, definitive diagnosis depends upon aortography. An aortogram should be obtained on all patients with any of these signs.—C. Peter Truog, M.D.

#### ABDOMEN

Marshak, Richard H., Janowitz, Henry D., and Present, Daniel H. Granulomatous colitis in association with diverticula. *New England J. Med.*, Nov., 1970, 282, 1080– 1084. (From: Department of Radiology and Medicine, Mount Sinai School of Medicine, New York, N. Y.)

The authors report 10 patients, 45 years of age or older, who were initially believed to have diverticulitis of the sigmoid and descending colon. These findings were made on both clinical and roentgenologic investigations. At operation the same diagnosis was entertained in 9 on the basis of gross findings. Pathologic examination of the resected specimens, however, revealed typical lesions of granulomatous colitis.

The history, physical examination and laboratory studies did not aid in the differential diagnosis except for the past history of perirectal disease in 4 patients. Analysis of the roentgenographic findings, however, revealed some distinguishing features, particularly the presence of a longitudinal, intramural fistulous tract, extending parallel to the lumen in the thickened bowel.

The authors conclude that this finding is pathognomonic for granulomatous colitis.—C. Peter Truog, M.D.

#### GENITOURINARY SYSTEM

Clément, J. P., Assadourian, R., Dufour, M., Juin, P., Debaene, A., and Legré, J. L'angiographie sélective rénale dans le bilan des lésions traumatiques des reins (à propos de 4 cas). (Selective angiography in the evaluation of renal traumatic lesions [report of 4 cases].) J. de radiol., d'électrol. et de méd. nucléaire, June-July, 1970, 51, 353–360. (From: Chaire de Radiologie, Hôpital de la Timone, 13-Marseille, France.)

Following a renal trauma, the assessment of operative indications is often difficult. The primordial factor to be considered in such cases is preservation of the kidney. An average of 5 per cent of cases requires urgent surgery because of serious hemorrhage which endangers life. In the remainder of cases, 2 courses of action are possible: early intervention, or slightly deferred operation. In the first instance, hemostasis is often laborious and kidney removal may be decided upon, even though the organ might be the site of reversible lesions. In the second eventuality, the goal of the surgeon is to evacuate effusions, to free the kidney and its ureter, to remove necrotic renal segments and thus avoid progressive atrophy culminating in a totally nonfunctional kidnev.

Renal injuries may be classified according to 3 anatomo-clinical types, as follows: (1) ruptured pedicle; (2) renal contusions without rupture of the excretory cavities; and (3) renal contusions accompanied by ruptured excretory cavities.

Clinically, hematuria is the revealing sign of a renal involvement. Its persistence, together with the presence of an increasing hematoma, constitute 2 important factors which will prompt an early surgical intervention.

Radiologic investigation will be restricted to intravenous urography during the phase of immediate urgency. It is most important to detect pre-existing anomalies. Parenchymal lesions will be revealed by pyelo-calyceal deformities. Rupture of the excretory cavities will be recognized by extravasation of the opaque medium.

A nonfunctioning kidney may correspond to 3 types of lesions: (1) simple functional inhibition; (2) obstruction of the excretory pathway; and (3) a ruptured pedicle.

Renal angiography provides a much more precise lesional evaluation and should be performed in the days following the emergency phase. Selective angiography is preferable to translumbar aortography if there are no clinical contraindications. Either the femoral or the axillary approach may be chosen. In any case, an aortography should complete the selective examination. This procedure will bring to evidence ectopic renal arteries and give a general ap-

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praisal of the abdominal vessels. Associated lesions in the liver or spleen will also be detected.

Roentgenologic findings: Angiographic phase. This reveals lesions of the renal artery and its main branches: stenosis, thrombosis or a rupture. In the peripheral small arteries, displacement or avascular areas will indicate parenchymal lesions.

Nephrographic phase. This is most reliable for the depiction of parenchymal injuries: simple fissure, cuneiform rupture, displaced renal fragments. Ruptured excretory cavities will be revealed by opaque medium escaping under the capsule or outside it.

Renal scannography may be indicated in the case of a nonfunctioning kidney.

Retrograde pyelography may also be performed. In this event, the catheter can be left in place to help localization of a rupture with an injection of methylene blue at the time of the operation.

The authors report 2 cases of renal contusions investigated by renal angiography a few days after a trauma. In one case a cuneiform parenchymal rupture was demonstrated, and in the second, a rupture of the artery leading to the lower pole was shown, with amputation and fragmentation of the lower pole in the nephrographic phase.

Two other cases investigated some years after a trauma presented severe renal atrophy with deformed renal cavities in one case, and in the other, an organized hematoma in the upper pole, accompanied by marked capsular thickening.—H. P. Lévesque, M.D.

Bollini, V., Bono, F., Bonomini, V., Capelli, A., Cecchetti, E., Corinaldesi, A., Laschi, R., Piccaluga, A., and Zucchelli, P. L'effetto delle radiazioni ionizzanti sul rene umano. (The effect of ionizing radiations on the human kidney.) Radiobiol., radioterapia e fis. med., July-Aug., 1969, 24, 225–244. (From: Istituto di Radiologia e del Radio "L. Galvani" della Università di Bologna, Italy.)

From 1906 to 1968 more than 160 cases of postradiation nephropathies have been reported. The classification by Luxton (1964) is the one most generally accepted: acute nephritis; chronic nephritis; benign hypertension; late malignant hypertension; proteinuria. These complications generally are demonstrated in patients irradiated with the abdominal bath technique.

Research conducted by the authors in the period 1966–1968 has demonstrated that in individuals subjected to radiotherapy of areas including the kidneys, an interstitial fibrosis of the parenchyma of the kidneys can occur, even in the absence of clinical or laboratory findings suggesting a nephropathy.

From a group of 417 patients treated in the Department of Radiology "L. Galvani" of the University of Bologna for various abdominal conditions,

excluding diseases of the kidneys, 54 cases irradiated because of neoplasm of the testicle were chosen for their research.

The early reactions appeared within 3 months of the radiation treatment in 7 patients, who were subjected to orthokinetic tomotherapy with Cs<sup>137</sup> over 2 opposite fields of 15×42 cm. size, with a total dose of 3,000 rads in 20 days. The late reactions, appearing between 4 months and 16 years after the treatment, were studied in 14 patients irradiated with 200 kv. tomotherapy and telecesium therapy.

Of the 7 cases presenting early reactions, anemia was noted in 2 cases, and leukocyturia also in 2 cases, while proteinuria, cylindruria and hypopotassemia were demonstrated in each of the 3 remaining cases. The excretory urographies, renal arteriographies, and renal scintigraphies were normal. Histologic studies of the biopsy specimens demonstrated that the early reaction of the kidney parenchyma was a glomerulopathy, although in the words of the authors "the exact definition of this glomerular alteration as well as its pathogenesis is unknown."

The late reactions were characterized by benign hypertension in 7 cases; in the other 7 cases proteinuria was present, 6 of whom also showed cylindruria, and in 1 of these 7 patients there was also evidence of microhematuria. In the great majority of the cases the glomerular filtrate and the values of the tubular function were normal. Only in a few cases was there a moderate reduction of the creatinine clearance. Excretory urographies were normal, while renal arteriographies showed an occasional alteration in the course and caliber of the intrarenal arteries, in particular in the lower half of the kidneys. Histologic studies by the electronic microscope of the biopsy specimens showed glomerular lesions which would appear to be an evolution of the lesions demonstrated in the cases presenting early reactions. The membranes of Bowman and the basal membranes of the capillaries were thickened, with diffuse proliferation of the so-called "basement membrane branches." The severity of this interstitial fibrosis was definitely related to the total radiation dose. It was noted that 88 per cent of the cases who received more than 2,500 rads to the kidneys presented a certain degree of fibrosis, while only 15 per cent of the cases who received lesser doses showed a similar degree of interstitial fibrosis.

The authors conducted a series of experiments in the rabbit to confirm these findings. The kidneys of the animals were irradiated for a total of 500-1,000 and 2,500 r from a source of Co<sup>69</sup>. The histologic studies confirmed the findings observed in the human kidneys subjected to irradiation.—A. F. Govoni, M.D.

#### SKELETAL SYSTEM

ROKKANEN, PENTTI, and JULKUNEN, HELJO. Bone changes in parathyroid adenoma: report of a case. *Acta orthop. scandinav.*, 1970,

41, 321-327. (From: Clinic for Orthopaedics and Traumatology, University Central Hospital, Helsinki, Finland.)

Following a pathologic fracture through a cyst in the fifth metacarpal, this area was resected and resembled a giant cell tumor histologically. On check-up other cysts were found and the patient had the roentgenologic and laboratory diagnosis of hyperparathyroidism with multiple cysts, osteoporosis and vertebral compression.

Two parathyroid adenomas were removed and I year later most of the bone changes had cleared.

Iliac crest biopsies were taken before and after surgery following bone labelling by oxytetracycline. Prior to surgery tetracycline fluorescence was seen in the margins of the trabeculae and I year later there was fluorescence in the large cancellous areas and also in the cancellous spaces indicating a regenerative process.

Microradiographs initially showed a thin bone network of low density with fragmentation and erosion of the margins of the trabeculae. On the second examination the trabecular margins were clearer, although some still had areas of erosion. Regenerative areas were visible in the cancellous spaces and there was less osteoid tissue. These studies showed that regeneration of bone continues after the cysts and evident osteoporosis have cleared. The bone changes in primary hyperparathyroidism are similar to those in osteomalacia.—M. E. Mottram, M.D.

Schajowicz, Fritz, and Lemos, Claudio. Osteoid osteoma and osteoblastoma: closely related entities of osteoblastic derivation. *Acta orthop. scandinav.*, 1970, 41, 272–291. (Address: Fritz Schajowicz, Head, Latin American Registry of Bone Pathology, Italian Hospital, Gascon 450, Buenos Aires, Argentina.)

The authors compare the findings in 142 cases of osteoid osteoma and 42 cases of osteoblastoma from the Latin American Registry of Bone Pathology. The distinction between these 2 lesions is not entirely clear and there is often difficulty in classifying the borderline cases. Evidence presented is that they are merely variants of the same lesion.

The following classification, identifying both lesions as osteoblastoma is preferred: (1) circumscribed osteoblastoma previously called osteoid osteoma and having a nidus less than 2 cm. in size. They are usually cortical with adjacent sclerosis but may be medullary or periosteal with little or no sclerosis; (2) genuine osteoblastoma with a nidus greater than 2 cm. in size. These are usually medullary with very little or no sclerosis but may be cortical with sclerosis; and (3) multifocal osteoblastoma, which may be central or peripheral.

In the Registry cases called osteoid osteoma, 50

per cent were aged 11-20 years and the femur and tibia were the most frequently involved bones. Twenty-one cases were medullary or subperiosteal and 18 of these had little if any perifocal reactive sclerosis. Twenty-five per cent of the cases had a dense central component and the rest had a radiolucent nidus usually less than I cm. in size and no greater than 2 cm. in size. In the Registry group of osteoblastoma more than 50 per cent were under 20 years of age and the spine had the greatest number of lesions. The evolution of these lesions appeared to be more rapid than the osteoid osteomata. Only a few patients had night pain relieved with aspirin. Some of these cases have been called "unusually large osteoid osteoma." Six of these cases had a periosteal origin. The histologic structure was similar to other osteoblastoma but the perifocal sclerosis was generally lacking.

The so-called multifocal sclerosing osteoblastoma is rare and has not been reported previously. The authors have seen 2 medullary and 2 peripheral cases. In each case there was more than one circumscribed nidus, all enclosed in a block of sclerotic bone. The peripheral (juxtacortical) lesions were located in the ethmoid and pubis. The 2 medullary (central) lesions were in the sacrum and humerus. The histologic picture was identical to that of osteoid osteoma surrounded by dense bone.

The histology of these cases is discussed in detail and is similar in both lesions. The differences between osteoid osteoma and osteoblastoma have been based on the structural organization with the circumscribed form (so-called osteoid osteoma) showing a more organized structure. A so-called osteoid osteoma may progress into an osteoblastoma. Two of the authors' cases had possible transformation of benign osteoblastoma into a low-grade osteosarcoma. The difference between the two types of osteoblastoma appears secondary to their location which explains the slow growth potential of the cortical circumscribed osteoblastoma and the more active growth of the genuine osteoblastoma.—M. E. Mottram, M.D.

DARGENT, M., COLON, J., LAHNECHE, B., and FESTA, A. Les métastases osseuses du cancer thyroīdien. (Bone metastases from cancer of the thyroid.) *Ann. de radiol.*, 1970, 13, 483-506. (From Centre Léon-Bérard de Lyon, 28, rue Laennec, 69-Lyon, France.)

The authors present a thorough study of bone metastases from thyroid carcinoma observed between 1922 and 1968. These cases are divided into 2 groups: a first group of 44 patients in whom bone metastases were diagnosed at the same time as the thyroid cancer; and a second group of 47 patients in whom bone metastases were discovered 6 months to 20 years after treatment of the primary lesion.

They evaluate these cases according to the following factors: (a) the host factor (sex ratio, age);

(b) the tumor factor; (c) the physiopathology of metastasis; (d) the clinical aspects and radiologic appearance; and (e) the prognosis and therapeutic possibilities.

The results must be interpreted with caution, observing the prolonged spontaneous evolution of certain forms and especially the intricate effects of successive treatments.

Among the therapeutic procedures, the authors attribute an important role to hormonal substitution therapy in cases showing a favorable evolution.—

H. P. Lévesque, M. D.

Weston, W. J. The bursa deep to tendo Achillis.

Australasian Radiol., Aug., 1970, 14, 327-331. (From: Hutt Hospital, Lower Hutt, New Zealand.)

The bursa beneath the Achilles tendon caps the posterosuperior angle of the os calcis. The radio-lucent shadow here represents the 2 layers of extrasynovial fat around the sub-Achilles bursa. The earliest change of Achilles bursitis is swelling of the soft tissues so that the clear space beneath the tendon occupied by fat becomes opaque due to inflammatory cells, fluid, edema and synovial hypertrophy.

Two cases with severe rheumatoid arthritis are reported, both showing an enlarged sub-Achilles bursa on the lateral soft tissue projections of the heels.—M. E. Moitram, M.D.

#### BLOOD AND LYMPH SYSTEM

CITRON, B. PHILIP, HALPERN, MORDECAI, MC-CARRON, MARGARET, LUNDBERG, GEORGE D., McCORMICK, RUTH, PINCUS, IRWIN J., TATTER, DOROTHY, and HAVERBACK, BERNARD J. Necrotizing angiitis associated with drug abuse. New England J. Med., Nov., 1970, 283, 1003-1011. (From: Departments of Medicine, Radiology and Pathology, Los Angeles County—University of Southern California Medical Center, Los Angeles, Calif.)

Fourteen young drug abusers with a necrotizing angiitis indistinguishable from periarteritis nodosa were studied. The 6 women and 8 men had used narcotics, stimulants, hallucinogens and depressants. Methamphetamine, alone or in combination with heroin or d-lysergic acid diethylamide, was used commonly.

The clinical presentation varied from a complete lack of symptoms in 5 patients to pleomorphic sys-

temic signs and symptoms with renal failure, hypertension, pulmonary edema and pancreatitis.

Selective renal and visceral angiography has been crucial in the diagnosis of necrotizing angiitis. The vascular changes of necrotizing angiitis including arterial aneurysms and sacculations were noted in the kidney, liver, pancreas, and small bowel at selective angiography.

Postmortem findings in 4 patients revealed generalized vascular changes in differing stage including chronic and healed lesions. The diseased vessels included medium-sized and small arteries in most organs and arterioles in the brain. Elastic arteries, capillaries, and veins were spared. The histologic picture is indistinguishable from that of classic periarteritis nodosa and does not resemble hypersensitivity angiitis in which small arteries, capillaries and venules are involved.

Because of the multiplicity of the injected substances with a high probability of contamination, the exact etiologic agent in these cases is not clear; however, methamphetamine appears to be a common denominator.—W. T. McLaughlin, M.D.

ROTHFIELD, NEVILLE J. H. Fibromuscular arterial disease: experimental studies. Australasian Radiol., Aug., 1970, 14, 294–297. (From: Department of Radiology, University of Michigan, Ann Arbor, Mich., and Wayne County General Hospital, Eloise, Mich.)

The etiology and pathogenesis of fibromuscular dysplasia remain obscure despite a variety of experimental approaches designed to produce it in animals.

The author reviews all these techniques with special emphasis on stretching of the renal artery and his own method of producing the angiographic and pathologic changes of fibromuscular hyperplasia in dogs. Unfortunately, the angiographic appearances of beading and segmental narrowing following stretching of the renal artery are not progressive and are noted to resolve on serial studies.

Other experimental approaches include production of turbulence within vessels, hormonal supplements in animals with stretched arteries, production of dissecting aneurysm and denervation of the renal artery.

This communication with its accompanying bibliography is of interest as it does review the current and past approaches of producing fibromuscular hyperplasia in the experimental animal.—Robert I. White, Jr., M.D.



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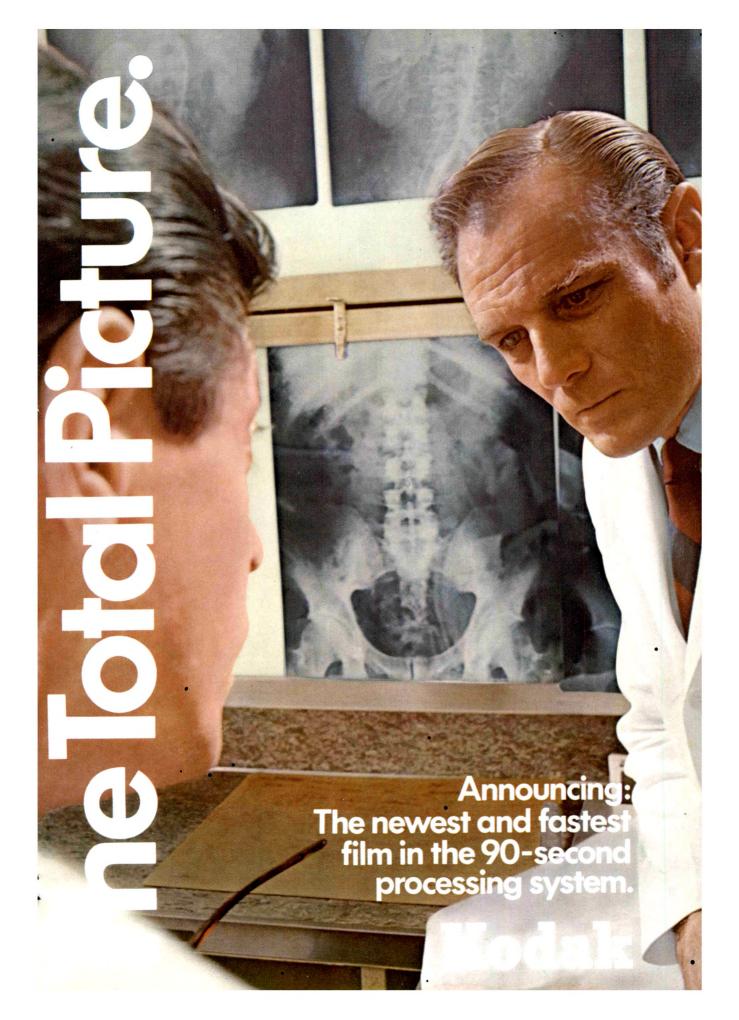
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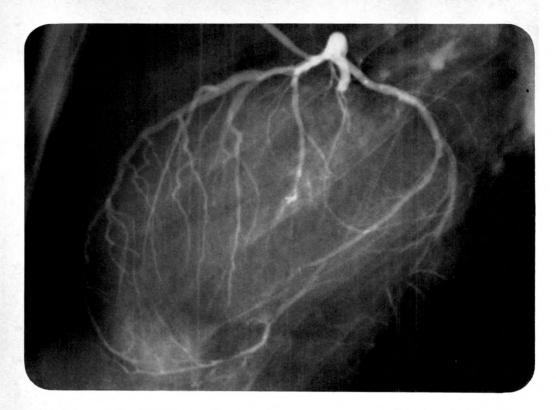
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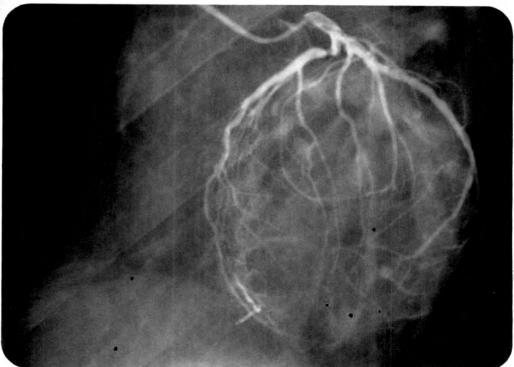
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Its high speed makes it ideally suited for examinations where patient motion may be a problem—as in pediatric radiology. It can also be used in applications requiring direct exposure examinations of extremities. And, KODAK RP ROYAL X-OMAT Medical X-ray Film is especially effective for use with portable x-ray equipment. Its special surface coating gives it reliable transport in rapid film changers.

Ask your Kodak Technical Sales Representative—or your dealer—to demonstrate the dependable performance of the new KODAK RP ROYAL X-OMAT Film—and the other quality products in the Kodak 90-second system. Products that are made together to work together. For the total picture.

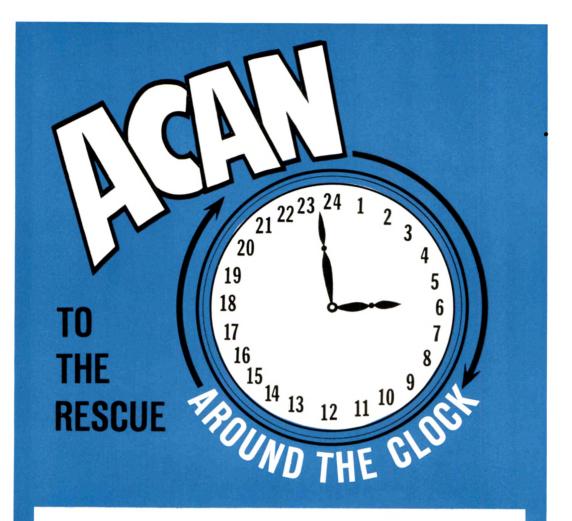
Kodak

\*Rapid Processing

EASTMAN KODAK COMPANY Radiography Markets Division, Rochester, New York



## Someone must be sure of something.\*



Trouble knows no time of day. X-ray processing equipment can become jammed or break down at any hour.

That's why Acan X-Ray has a 24-hour around-the-clock emergency repair service. Our skilled technicians are always on call to serve you whatever the time of day or night.

In addition to being available around-the-clock, Acan X-Ray also provides complete parts and inventory supply, as well as all major brands of concentrated and pre-mixed chemicals.

When you have a problem — or need fast service — call

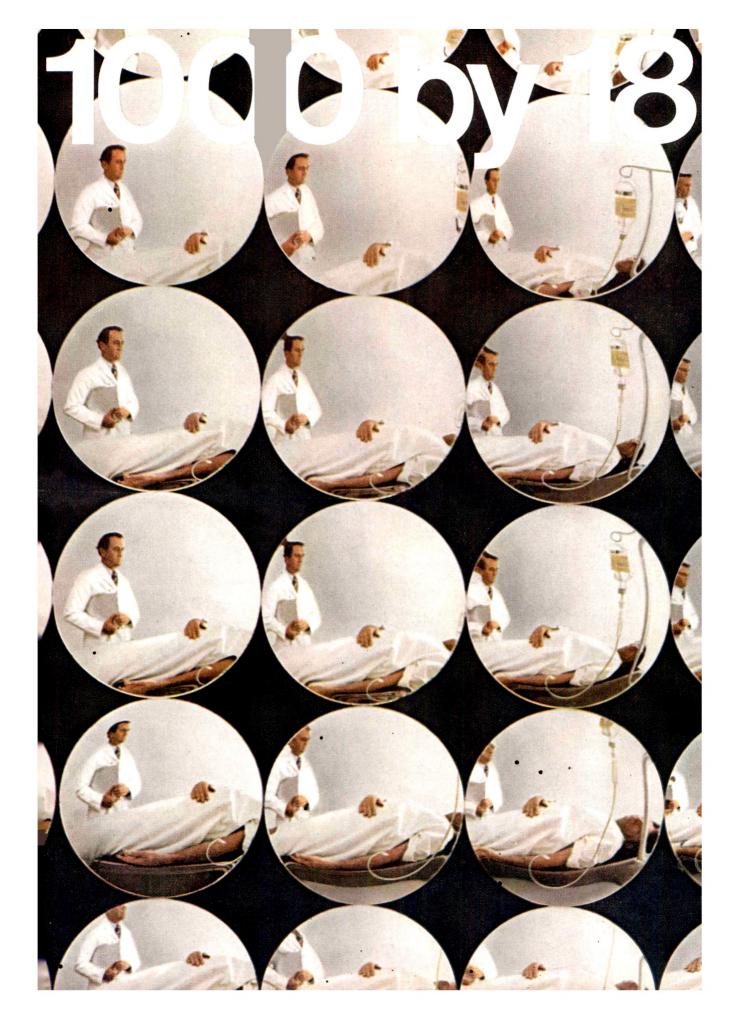
# ACAN X-RAY a subsidiary of

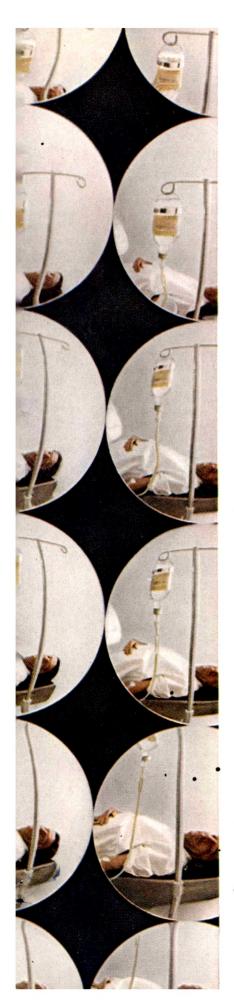


DETROIT, MICH. (313) 366-8100 NEW JERSEY (201) 863-6511 FLINT, MICH. (313) 686-1500 NEW YORK (212) 721-5252

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## Over 1000 examinations by 18 investigators prove the efficacy of drip infusion pyelography

# RENO-M-DIP™

Meglumine Diatrizoate Injection U.S.P. (30%-For Drip Infusion Pyelography)

The diagnostic effectiveness of drip infusion pyelography has been established in over 1000 radiologic examinations of individual patients by 18 independent investigators.<sup>1</sup>

In a composite of the 1,062 patients studied and reported upon, 87% showed excellent to good urograms. In these studies, 728 patients received a 1:1 dilution of a 60% solution of meglumine diatrizoate, and 334 received the ready-to-use 30% solution.

These studies also showed that not only are dense nephrograms obtained with the drip infusion pyelography procedure, but satisfactory cystograms are also provided. In addition, pictures of the ureter were definitive—usually with complete visualization on one film.

Drip infusion pyelography was used successfully even in cases with various degrees of azotemia—and in many instances was shown to avoid the need for retrograde pyelography.

#### Better visualization

Improvement over regular I.V. pyelography was shown specifically in 89.5% of 180 cases by 8 of the 18 investigators.<sup>1</sup>

#### Adverse reactions

Adverse reactions were generally mild and occurred in 6.7% of the cases. The most frequent reactions were nausea and urticaria (see brief summary on next page). (All meglumine diatrizoate solutions used were equivalent to 30% concentration.)

#### A convenient bottle

The bottle containing Reno-M-DIP is calibrated, to make dosage measurement easy. It has a standard screw-neck that accommodates all the usual attachments. It will take any top—screw-top, needle or spike.

Drip infusion pyelography is a simple, reliable, and relatively safe procedure for diagnosis of urologic disease process. Use Reno-M-DIP whenever drip infusion pyelography is indicated.

1. Data on file at The Squibb Institute for Medical Research. See next page for brief summary.

#### **SQUIBB**

# Whenever drip infusion pyelography is indicated

## RENO-M-DIP

Meglumine Diatrizoate Injection U.S.P. (30%-For Drip Infusion Pyelography)

Reno-M-DIP<sup>TM</sup> (Meglumine Diatrizoate Injection U.S.P.) for drip infusion pyelography provides a sterile, aqueous solution of 30% meglumine diatrizoate which contains approximately 14% (42.3 grams per 300 cc.) bound iodine and 0.04% disodium edetate as a sequestering agent. The solution contains approximately 0.054 mg. (0.002 mEq.) sodium per cc. (16.2 mg. per 300 cc.).

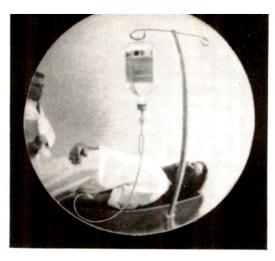
Contraindications: Contraindicated in persons hypersensitive to salts of diatrizoic acid. Urography is contraindicated in patients with anuria.

Warnings: A definite risk exists with the use of contrast agents in excretion urography in patients with multiple myeloma. There has been anuria with progressive uremia, renal failure and death. This risk of the procedure in these patients is not a contraindication; however, partial dehydration in preparation for study is not recommended since it may predispose for precipitation of myeloma protein in renal tubules. No therapy, including dialysis, has been successful in reversing this effect. Myeloma should be considered in persons over 40 before undertaking urographic procedures.

In cases of known or suspected pheochromocytoma, if the physician feels that the possible benefits outweigh the considered risks, radiopaque materials should be administered with extreme caution; however, an absolute minimum of material should be injected, the blood pressure should be assessed throughout the procedure, and measures for treating a hypertensive crisis should be available.

Contrast media may promote sickling in homozygous individuals when injected I.V. or intra-arterially. Although a history of sensitivity to iodine *per se* or to other contrast media is not an absolute contraindication, administration of meglumine diatrizoate requires extreme caution in such cases. Meglumine diatrizoate should be used in pregnant patients only when the physician deems its use essential to the welfare of the patient since safe use during pregnancy has not been established. Perform thyroid function tests prior to administration of meglumine diatrizoate since iodine-containing contrast agents may alter the test results. Perform urography with extreme caution in persons with severe concomitant hepatic and renal disease.

Precautions: Diagnostic procedures involving use of contrast agents should be performed under the direction of personnel with prerequisite training and a thorough knowledge of the particular procedure. Appropriate facilities should be available for coping with situations which may arise as a result of the procedure and for emergency treatment of severe reactions to the contrast agent itself; competent personnel and emergency facilities should be available for at least 30 to 60 minutes after I.V. administration since delayed reactions have been known to occur. These severe life-threatening reactions suggest hypersen-



sitivity to the contrast agent. A personal or family history of asthma or allergy or a history of a previous reaction to a contrast agent warrants special attention and may predic more accurately than pretesting the likelihood of a reaction although not the type nor severity of the reaction in the individual. The value of any pretest is questionable. The pretest most performed is the slow injection of 0.5-1.0 cc of the preparation which may be given through the needle to be used for the full dose. If no reaction occurs within 15 minutes, the full dose may be given; however, this does not preclude the possibility of reaction. Should the test dose produce an untoward response, the necessity for continuing the examination should be reevaluated. If deemed essential, examination should proceed with all possible caution. In rare instances, reaction to the test dose may be extremely severe; therefore, close observation and facilities for emergency treatment are indicated.

Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by urographic agents; therefore, if known or suspected hepatic or biliary disorder exists, administration of meglumine diatrizoate should be postponed following the ingestion of cholecystographic agents. Consider the functional ability of the kidneys before injecting meglumine diatrizoate.

The recommended rate of infusion should not be exceeded. The diuretic effect of the drip infusion procedure may hinder an assessment of residual urine in the bladder. Adequate visualization may be difficult or impossible in uremic patients or others with severely impaired renal function (see Contraindications).

Adverse Reactions: Reactions most frequently encountered with drip infusion pyelography are nausea and urticaria. Chills, metallic taste, vomiting, dizziness, a rise or fall in blood pressure, itching, flushing, or generalized feeling of warmth, sneezing, etc. may occur and, rarely, may be severe enough to require discontinuation of dosage. Severe reactions which may require emergency measures (see Precautions) are a possibility and include cardiovascular reaction characterized by peripheral vasodilatation with hypotension and reflex tachycardia, dyspnea, confusion, and cyanosis progressing to unconsciousness. An allergic-like reaction ranging from rhinitis or angioneurotic edema to laryngeal or bronchial spasm or anaphylactoid shock may occur. Temporary renal shutdown or other nephropathy may occur. Intravenous injection of meglumine diatrizoate in a more concentrated formulation has produced a few instances of a burning or stinging sensation and of venospasm or venous pain.

Supply: Bottles of 300 cc. © 1971 E.R. SQUIBB & SONS. INC.

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Everybody knows Mavig®aprons. They know that Mavig offers greater flexibility, more protection, a more comfortable fit and a great selection of colors. (Including Mavig's popular True Blue.)

They know that only Mavig makes the *entire* apron (including the shoulder area) of the same protective material, giving overall protection and more even weight distribution. They know that only Mavig makes a special procedures model for both front and back protection.

•And they know that only Mavig offers three kinds of closures: snaps, velcro and the new string type.

But what they don't know is that Mavig aprons are now distributed by Keuffel & Esser X-Ray, Inc. And that you can now get just the Mavig apron you need by ordering direct from your dealer, or by calling us. Keuffel & Esser X-Ray, Inc., 20 Whippany Road, Morristown, New Jersey 07960. 201 285-5304.

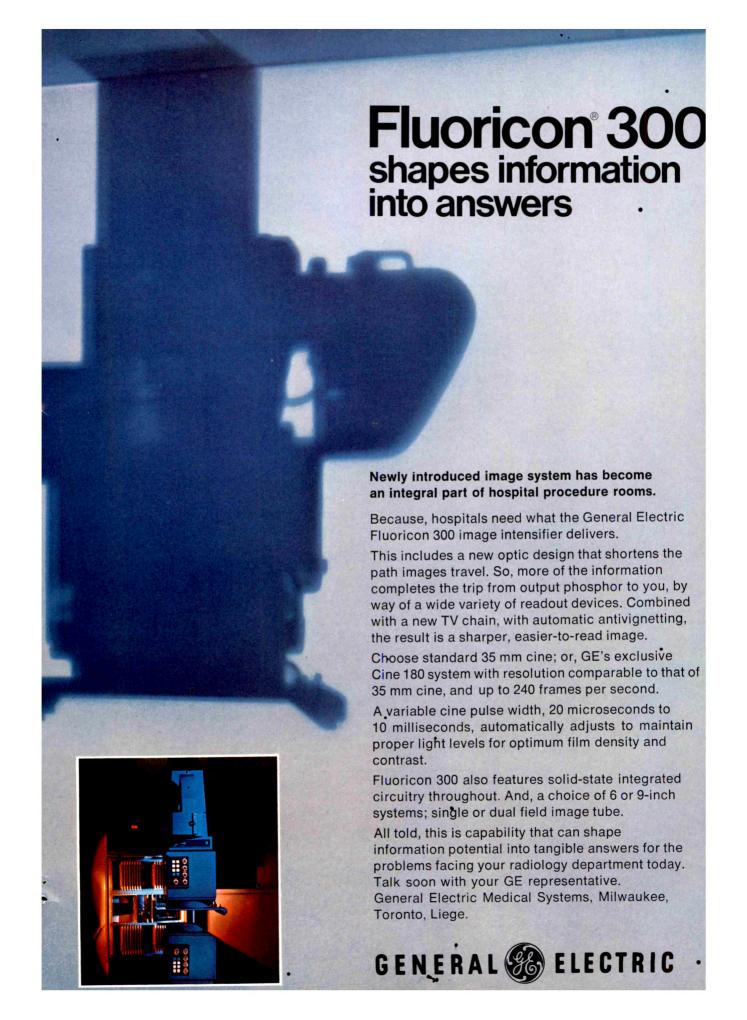
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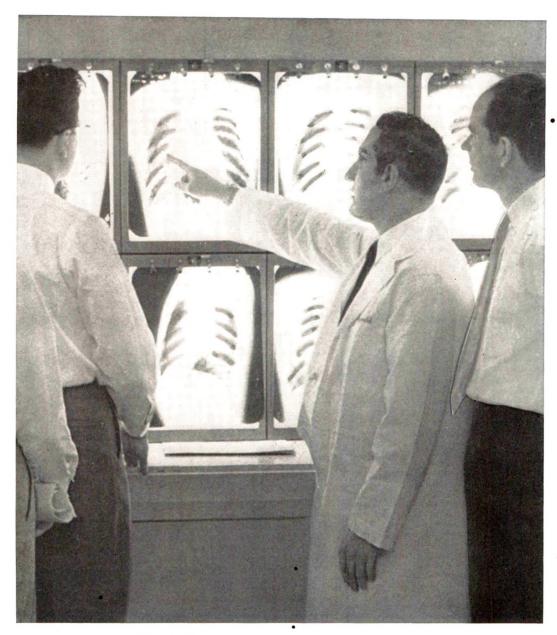




# Chest Radiography?

- 1. Would you like to handle more patients in less time?
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- 5. Would you like superior diagnostic quality?
- **6.** Would you like to verify film quality more promptly, and minimize waiting room congestion?
- 7. Would you like to free more experienced personnel for more demanding jobs?
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- 9. Would you like to eliminate film misidentification?
- 10. Would you like more information?

	-
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Quality made us worldwide, not our price.



Dealers of Fuji Kx and Rx film in all cities of the United States.

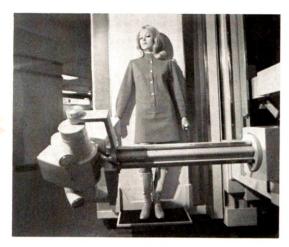


# Showdown

Telegem 90 remote capability demonstration



## kept doctors crowding around for more







GE INNOVATION IN RETROSPECT

Radiologists got their first look at General Electric's new Telegem 90 diagnostic x-ray system during the 1970 RSNA meeting. And they apparently liked what they saw . . . total-remote systems capability for ending patient-load problems.

Telegem 90 integrates TV fluoroscopy, radiography and linear tomography in a single room . . . and makes your return to tableside unnecessary. You sit at a shielded, remote console—all controls within easy reach—and shed the lead you'd otherwise wear.

The system is powered by GE's new MSI<sup>™</sup>-1250 generator. It features millisecond interrogation and phototiming accurate down to two milliseconds. For scanning, the intensifier moves through 20 inches, fast enough to follow a single barium swallow. Bucky radiography programs multiple image formats up to 6 on 1.

New multidirectional tubehead angulations let you peek around either side, plus head and foot angles, without disturbing your patient. Permits views of obscured areas or previously inaccessible structures.

And there's much more . . . that you really should see for yourself. Let us demonstrate Telegem 90's capability by scheduling a showing of our 10-minute RSNA exhibit motion picture. Your GE representative can arrange a viewing to fit your schedule. General Electric Medical Systems, Milwaukee, Toronto, Liege.

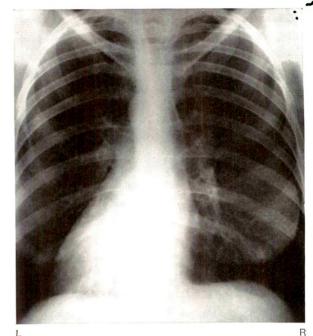




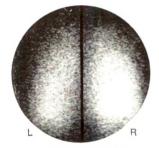
## STANDARD CHEST RADIOGRAPH. INVERTED AP VIEW.

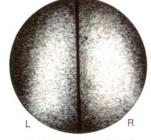
THE PHO/GAMMA SCINTILLATION CAMERA.

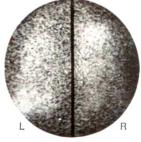


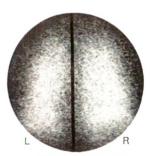


SERIAL SCINTIPHOTOS. POSTERIOR VIEW.









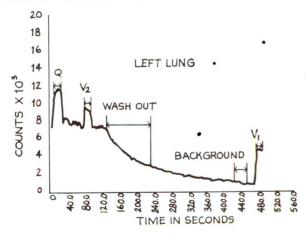
1. PERFUSION (Q)

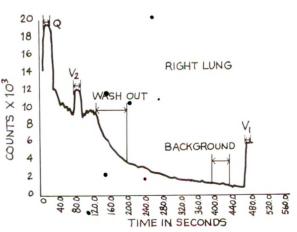
2. LUNG VOLUME (V2)

3. WASH-OUT

4. VENTILATION (V1)

#### TIME-ACTIVITY HISTOGRAMS.







### Th Pulmonary Study

### Evaluation of Pulmonary Perfusion and Ventilation with the Nuclear-Chicago Pho/Gamma® Scintillation Camera

This technique for dynamic regional pulmonary evaluation uses 133Xenon and the Pho/Gamma Scintillation Camera. The camera is equipped with the diverging hole collimator, allowing the entire lung field to be visualized.

SETTING-UP. The collimator is placed against the posterior thorax. Positioning flexibility of the Pho/ Gamma detector permits this study to be performed with the patient in either the upright or supine position, thus accommodating even the patient with limited or no mobility.

ISOTOPE AND DOSE. The clinician administers 30 mC of <sup>133</sup>Xe in sterile solution intravenously as a bolus injection to an antecubital vein. The patient exhales the xenon into a spirometer; he also rebreathes from the spirometer, thus providing data for determination of ventilation.

DATA ACCUMULATION. Serial scintiphotos are taken in the divided output mode, each representing approximately 60,000 counts in a 10-15 second period. (Note that Pho/Gamma can be operated on either a preset-time, preset-count, or preset-time/count basis as desired.) Also, as illustrated, time-activity histograms were made using a dual-channel ratemeter/dual-pen chart recorder.

If desired, this data could have been recorded in high-resolution digital form, on the Nuclear-Chicago Data-Store/Playback Accessory, or in digital form on the CDS-4096 Clinical Data System. Both of these system accessories allow stored patient data to be replayed, processed and manipulated in a variety of ways to produce additional qualitative and quantitative data.

EVALUATION. For comparison purposes, the standard chest radiograph on the opposite page shows a patient presented with mild dyspnea. The four serial scintiphotos illustrate the various stages of the pulmonary study. Finally, the recorder plots of each lung constitute time-activity histograms of a complete 8minute study.

In each histogram, the initial rise indicates passage of xenon into the lungs. Breath-holding at this time permits accumulation of data for determination of regional perfusion (Q, scintiphoto 1). Then, rebreathing from the spirometer to equilibrium is followed by a second deep breath to obtain data on lung volume (V2, scintiphoto 2). Wash-out follows on expiration (scintiphoto 3), after which a final deep breath is taken to determine regional ventilation of a single breath (V<sub>1</sub>, scintiphoto 4).

CONCLUSIONS. The several data presentations shown here demonstrate that in this case blood flow to the left lung is considerably less than to the right lung. The third scintiphoto shows an irregular pattern of delayed wash-out, characteristic of obstructive lung

This Pho/Gamma 133Xenon technique has been routinely performed on a large number of patients with a variety of lung disorders. It is felt that this data, when augmented with other diagnostic information, will assist the physician in making more definitive diagnoses. The results illustrate the severity of the disease states to be evaluated as well as the effectiveness of treatments indicated for the specific disorder.

### **Nuclear Reviews**

MOVIES (AND MORE) FOR DYNAMIC STUDIES. Add our Super-8/Persistence Scope Accessory to the Pho/Gamma. Then: (1) See live "fluoroscopic-type" view of dynamic phenomena on the persistence scope. (2) Record the study with the Super-8 movie camera at frame rates up to 32/second. (3) Replay all or part of the study in slow, fast, or stop-action with the Super-8 projector. (4) Receive more information from every dynamic study.

The Super-8 camera uses easy-to-load cassettes, has auto-exposure control. The persistence scope swivelmounts on the Pho/Gamma console. Included-a special projection screen. Ask for the full story.

IMAGE-DATA STORAGE, DISPLAY, AND MANIPULA-**7ION.** All you need to know about doing all of these things with the Pho/Gamma is in two new brochures. One talks about our Clinical Data System. The other covers our Data-Store/Playback Accessory. Shouldn't you have a copy of each? Writing to us makes it possible.

DOSE-CALIBRATION AND IN-VITRO COUNTING. Our Mediac® Radioisotope Dose Calibrator. And our Model 4454 In-Vitro Well Counting System. Their names tell you what they do. How they do it is fully explained in our literature. Yours for the asking.

An exchange of information on topics



which has more than a passing interest in

### **DuPont Announces a** Major Advance in Radiography...

. . . a revolutionary new way to handle sheet film. under daylight conditions and untouched by human hands.

### Here is what the Daylight System will do for your X-ray department.

- 1. Increase sheet-film handling speed, convenience, dependability
- 2. Improve patient care and
- 3. Eliminate some darkrooms 8. Low investment
- 4. Increase efficiency, capacity
- 5. Improve Diagnostic Clarity
- **6.** Provide positive patient identification
- 7. Simple, quick to install

### **Brief summary of the Daylight System**

### 1. Fast Film Handling

The Du Pont Daylight System provides fast, automated handling of sheet film, in any of the popular sizes, from package through processing, under daylight conditions. untouched by human hands. Here is how: 100 sheets of film are loaded in a film dispenser in about a minute. The dispenser, in turn, loads special cassettes in three seconds. A pull of a crank does the trick. Now, make the exposure, using present technics. The RT then unloads the cassette into a nearby special storage-feeder or directly to the processor. Results: Fast handling, great convenience.

### 2. Improved Patient Care and Flow

This efficient film handling system reduces interruptions to RT/patient contact. Lugging cassettes to the darkroom is greatly reduced. Loading and unloading film by hand become bygone chores. The time saved is spent in patient contact. Also, since film handling is now much faster and easier, examinations are completed more rapidly and patient flow is speeded.

### 3. Eliminate Darkroom

Some darkrooms can be eliminated since the Daylight System allows RTs to load packaged film in the dispenser, load film into cassettes, and process films—all in daylight conditions. The processor does not have to be in a darkroom; it can be elbow-close to the diagnostic room. This system, with various processing options, will handle one sheet at a time, or it can accumulate any number up to 50 exposed sheets and process them automatically. Again, all in daylight.

### 4. More Work in Same Space

This increase in film-handling speed will increase efficiency and capacity. How much depends upon your individual operation. Some people estimate up to a 30% improvement

in efficiency. Therefore, you may not have to expand your department physically to handle an increased workload.

### 5. Improved Diagnostic Clarity

This comes with the reduction of kinks, finger marks, dust contamination, soiled or stained screens. The Daylight System handles film more carefully than humans can. Another way the Daylight System will give improved diagnostic clarity is through improved film/screen contact. A unique spring-pressure system helps get you clearer, sharper radiographs than usually come from conventional cassettes.

### 6. Positive Patient Identification

An identification card, quickly prepared by your admitting personnel, slides into the cassette. The information records directly on the film for positive, permanent record without risk of mixup.

### 7. Easy Installation

The Daylight System is quickly and easily installed. Little or no architectural changes required. Conventional 110 volt A.C. is used. Only the film dispenser is wall-mounted, the rest of the equipment is easily moved into position.

### 8. Low Investment

Each component of the Daylight System has been carefully enginæred and precision built to give you high value-in-use at a low investment.

### Want to know more?

Kindly contact your Du Pont Technical Representative and he will show you all the details of how to adapt the parts of this system to your floor plan. He will help you estimate what the Daylight System can do for you. If you like what you see, he will arrange a "live" demonstration. These steps will enable you to make a sound decision easily.







### Du Pont introduces . . .

# The CRONEX\* Daylight Chest Changer

—a fast, automatic unit that gives full daylight operation at low cost . . . plus quick, easy installation.

If you're considering the purchase of a chest changer, you should be sure to see the unique combination of features offered by the new CRONEX Daylight Chest Changer.

### Automatic Daylight Operation Gives Optimum Convenience.

You get ready-to-read films, transported without touch of human hands from unopened package through processor. You can actually eliminate a darkroom. No need to buy another processor. Our unit utilizes your present processor after only minor modifications.

### The Operating Mechanism Is Simplicity Itself.

For example, gravity is used to aid film transport. The CRONEX Daylight Chest Changer works from top to bottom. One hundred sheets (14" x 17") are daylight loaded in the top (a one-minute job). Up to 50 exposed films are collected in a light-tight container in the bottom. This container, when transferred to your processor, feeds the exposed films automatically.

### Diagnostic Clarity Is Superb.

A unique spring-pressure system delivers superior film/screen contact. Automatic handling reduces artifacts (dirt, dust, kinks, fingermarks). You get excellent radiographic quality every time.

### Installation Is Quick and Easy.

Usually completed in a matter of hours. No structural changes required. 110 volt A. C. is used. Minimum room size: 5' x 12' with an 8-foot ceiling is all that's needed.

### Priced for High Value-in-Use.

Balancing your needs against performance of the new CRONEX Daylight Chest Changer, you'll see low initial cost with a high operational return on investment.

### Plus . . . Many Special Features.

Patients are positioned by a smooth, safe elevator. X-ray tube and exposure area remain stationary. Positive patient identification on film. Unit can be used with stereo. Any Du Pont film/screen combination works perfectly. No technic changes needed.

### Want to Know More?

Call your Du Pont Technical Representative. He'll fill you in on details and arrange a live demonstration. After that, your buying decision will be easy.

\*CRONEX is Du Pont's trademark for its X-ray films, screens, chemicals and equipment.





# radioisotope scanning Coming June 28, 1971 to Los Angeles.\*

Delay purchase or delivery of either a scanner or camera if you can. Unique new Elscint videoscanner, options and advanced ideas reflect a 3-year consensus of "what doctors want" for better, faster, easier-to-use isotope diagnostics.

For example:

Four distinct digital readout modes (including optional vivid electronic color display with solid state memory, without ribbons or filters...interfaces to any scanner!).

"Zero reference point" digital probe location.

Pushbutton window selection of nine ranges, with automatic lock on peak.

Automatic control of film exposure density, contrast and

speed, using minimum and maximum settings.

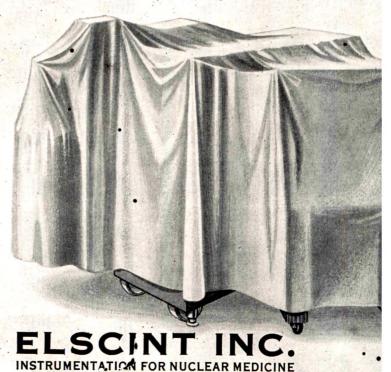
Solid state scalers with burnout-proof display digits.

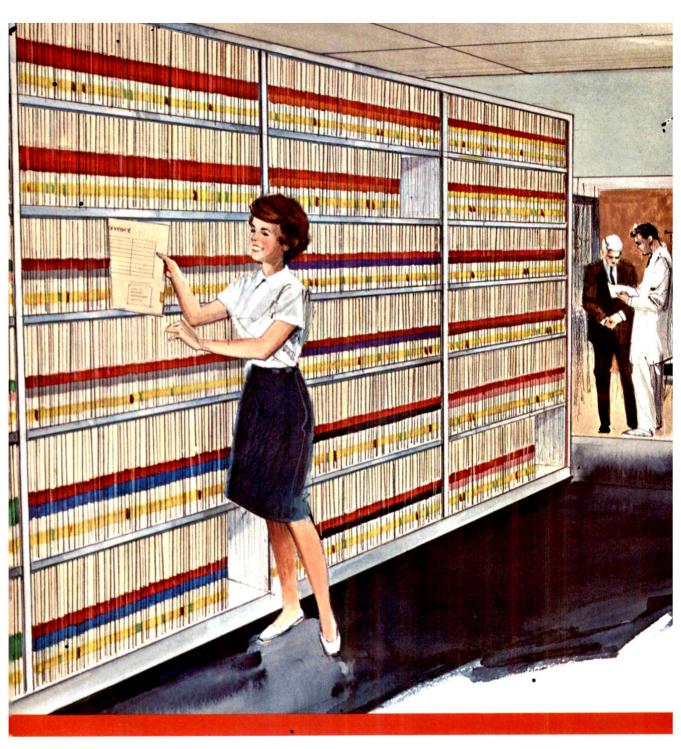
All U.S. made components.

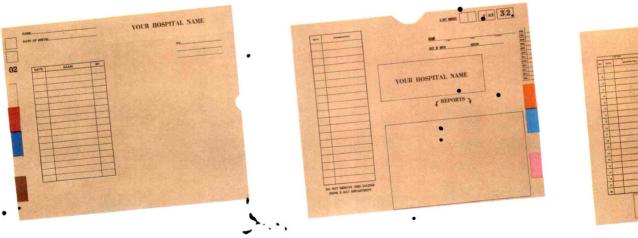
"Now" service, nationwide.

And new breakthroughs we can't even hint about yet!

\*Society of Nuclear Medicine, \*
18th Annual Meeting, Los Angeles,
June 28-July 2, 1971.









# AMES COLOR-FILE eliminates mis-files in the Radiology Department

### Color Coded X-Ray Jacket

Two standard sizes are available:

14¾" x 18¼" open side 14¾" x 17¾" open end

Made from a durable tag, these jackets are printed in 10 colors in either two positions or three positions for terminal digit filing. The year code is also printed in color. Jackets are either pre-numbered with full unit number (when x-ray department issues its own number) or terminal digits only (when x-ray department uses hospital unit number). Terminal digits only may also be printed for use with Social Security numbers. Special pockets may be attached for reports.

### Also available:

- · Special sizes and styles
- "Teaching File" pockets available in various colors
- Expansion pockets for volumes; size 14¾"
   x 18¼" x 1"
- · Open shelf guides
- Out guides



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□ <sub>●</sub> X-Ray jackets	<ul><li>Out guides</li></ul>			☐ Radiation therapy jackets			
☐ Standard folders	<ul><li>Special folders</li></ul>			<ul><li>Consulting services</li></ul>			
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Institution							
Address							
City		•	State			Zi	p • •

### Introducing our 1971 model Sanchez-Perez.



### Unfortunately, it's the same as our 1948 model.

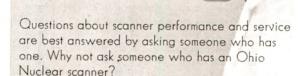
Honestly, we've tried to improve it. But that's a lot easier to talk about than it is to do. The original design was so blasted simple, so reliable, so trouble-free, so dependable, it's enough to drive our engineers up the wall.

Oh, they've made a few small improvements here, a couple of changes there, but nothing really significant. For a while, they thought about changing the color every year, but wiser heads prevailed. The Sanchez-Perez Automatic Seriograph remains the best—and only—film changer in its price class.

Last month, we suggested to our engineering department that they spend their time trying to find a way to build the Sanchez-Perez to sell for the same price we charged in 1948. We'll let you know how that comes out.

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Cerebral Angiography

Hypaque meglumine 60%, as a pure meglumine diatrizoate, offers an advance in contrast studies of the cerebral vasculature because of its excellent vascular tolerance.



Excretory Urography

Hypaque meglumine 60% provides highly diagnostic urographic contrast, particularly at doses of 50 to 60 ml. in adults, with excellent tolerance.



Peripheral Angiography

(Venography and Arteriography)

Hypaque meglumine 60% provides well-defined arteriograms and venograms for accurate diagnosis, with the advantage of excellent vascular tolerance and low systemic toxicity, when introduced into the venous or arterial systems.

# Hypaque meglumine 60% meglumine diatrizoate, USP



### GENERAL CONTRAINDICATION

Bnef Summary:

GENERAL CONTRAINDICATION

Do not use Hypaque meglumine 60 per cent solution for myelography. Injection of even a small amount into the subarachnoid space may produce convulsions and result in fatality.

GENERAL WARNINGS

Use in Pregnancy. No teratogenic effects attributable to Hypaque meglumine 60 per cent have been observed in reproduction studies in animals. However, before administration of Hypaque meglumine 60 per cent to women of child-bearing potential, the benefit to the patient should be carefully weighed against the possible risk to the fetus. In addition, most authorities consider elective contrast radiography of the abdomen contraindicated during pregnancy.

Administration of radiopaque materials to patients known or suspected to have pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the amount of radiopaque material injected should be kept to an absolute minimum. The blood pressure should be assessed throughout the procedure, and measures for treatment of a hypertensive crisis should be available. should be available.

Contrast media have been shown to promote the phenomenon of sickling in individuals who are homozygous for sickle cell disease when the material is injected intravenously or intraarterially.

of sickling in individuals who are homozygous for sickle cell disease when the material is injected intravenously or intraarterially.

GENERAL PRECAUTIONS

Before a contrast medium is injected, the patient should be questioned for a history of allergy. Although a history of allergy may imply a greater than usual risk, it does not arbitrarily contraindicate the use of the medium. Premedication with antihistamines to avoid or minimize possible allergic reactions may be considered. Diphenhydramine hydrochloride (i.e., Benadryi\*), however, should not be mixed in the same syringe with Hypaque meglumine since it may cause precipitation. The injection of 0.5 to 1 ml. of the contrast medium intravenously approximately 15 minutes prior to injection of the full dose is frequently used in an effort to screen patients. The absence of a reaction to this test dose is not entirely reliable for predicting the patient's response to the full diagnostic dose. Severe reactions, including fatalities, have occurred with a test dose as well as with larger doses. Adequate facilities for treating severe reactions should be available.

Caution is advised in patients with severe cardiovascular disease, hyperthyroidism, extreme seniility (but not old age per se), and in patients with a history of bronchial asthma or other allergic manifestations, or of sensitivity to iodine.

Water-soluble iodinated radiopaque media will cause a marked elevation of the protein-bound iodine (PBI) level and possibly a false low iodine uptake result up to 48 hours after their use. Therefore, thyroid function studies (PBI and 24-hour radioiodine uptake levels) should be performed prior to radiographic studies, if clinically indicated.

GENERAL ADVERSE REACTIONS

Reactions accompanying the use of contrast media may vary

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Reactions accompanying the use of contrast media may vary directly with the concentration of the substance, the amount used, the technique used, and the underlying pathology.

The following have been reported after administration of diatrizoates and other iodinated contrast media. Reactions due to technique: hematomas and ecchymoses. Hemodynamic reactions: vein cramp and thrombophlebitis following intravenous injection: Cardiovascular reactions: rare cases of cardiac arrhythmias, hypertension, hypotension and shock, and cardiac arrest. Occasionally, transient proteinuria, and rarely, oliguria or anuria. Allergic reactions: asthmatic attacks, nasal and conjunctival symptoms, dermal reactions such as urticaria, and rarely, anaphylactic reactions. Signs and symptoms related to the respiratory system: pulmonary or laryngeal edema, bronchospasm; or to the nervous system: restlessness, convulsions. Other reactions: flushing, pain, warmth, nausea, vomiting, anxiety, headache, and dizziness. Infrequently, "iodism" (salivary gland swelling) from organic iodinated compounds appears two days after exposure and subsides by the sixth day.

### CEREBRAL ANGIOGRAPHY

Indication: Hypaque meglumine 60 per cent may be administered for visualization of the cerebral vessels. Inasmuch as cerebral angiography is a highly specialized procedure requiring the use of special techniques, it is recommended that Hypaque meglumine 60 per cent be used for this purpose only by persons skilled and experienced in carrying out the procedure.

Contraindication: Carotid angiography during the progressive period of a stroke should be avoided, particularly on the left side because of the increased risk of cerebral complications.

Precautions: See Section on General Precautions.
Patients in whom cerebral angiography is to be performed should be selected with care.

should be selected with care.
Although cerebral angiography has been considered contraindicated in patients who have recently experienced cerebral embolism or thrombosis (stroke syndrome), many experts now believe that the diagnostic value of the procedure, when employed early as an aid in locating lesions amenable to operation, outweighs any added risk to the patient. Furthermore, a small number of post-angiographic fatalities have been reported, including progressive thrombosis already clinically evident before angiography, in which the procedure did not appear to play any direct role. Patients with severe cerebrovascular disease should be examined primarily by indirect methods of angiography.

severe cerebrovascular disease should be examined primarily by indirect methods of angiography.

In cerebral angiography, every precaution must be taken to prevent untoward reactions. Reactions may vary directly with the concentration of the substance, the amount used, the speed and frequency of injections, and the interval between injections.

In subarachnoid hemorrhage, angiography is expected to be hazardous. In migraine the procedure can be hazardous because of ischemic complications, particularly if performed during or soon after an attack.

after an attack

Adverse Reactions: See Section on General Adverse Reactions With any contrast medium introduced into the cerebral vascu-lature, neurologic complications, including neuromuscular dis-orders, seizures, loss of consciousness, hemiplegia, unilateral dysesthesias, visual field defects, language disorders (aphasia), and respiratory difficulties may occur, particularly when the extent of the intrinsic lesion is unknown. Such untoward reactions are for

the most part temporary, although permanent visual field defects have been reported. Some investigators who are experienced in angiographic procedure emphasize the fact that they tend to occur after repeated injections or higher doses of the contrast medium. after repeated injections or higher doses of the contrast medium. Other clinicians find that they occur most frequently in elderly patients. Inasmuch as the procedure itself is attended by technical difficulties regardless of the risk the patient presents (e.g., mechanical catheter obstruction of the vertebral artery can cause transient blindness), the more experienced the radiologic team, the fewer

blindness), the more experienced the radiologic team, the fewer the complications of any degree that are apt to arise.

Dosage and Administration: A dose of 8 to 12 ml. injected at a rate not exceeding the normal flow in the carotid artery (about 5 ml. per second) is suggested. The dose may be repeated as indicated; however, an increased risk attends each repeat injection. Children require a smaller dose in proportion to weight. Light anesthesia may be required in these procedures.

PERIPHERAL ANGIOGRAPHY
(ARTERIOGRAPHY AND VENOGRAPHY)
Indication: Hypaque meglumine 60 per cent may be administered to establish the peripheral vascular status of the patient by means of peripheral arteriography or venography.
Percentillary Soc Soction Consolidations and Consolidation Societies.

Precautions: See Section on General Precautions.

Adverse Reactions: See Section on General Adverse Reactions.

Soreness in extremities has also been reported.

Dosage and Administration: Diagnostic arteriograms may be obtained with 20 to 40 ml. of Hypaque meglumine 60 per cent introduced into the larger peripheral arteries by percutaneous or operative methods. Visualization of veins in the extremities may be accomplished with 10 to 20 ml.

### **EXCRETORY UROGRAPHY**

Indication: Since Hypaque meglumine 60 per cent is rapidly eliminated by the kidneys in radiopaque concentration, its use is indicated for excretory urography.

**Precautions:** See Section on General Precautions. Some clinicians consider multiple myeloma a contraindication Some clinicians consider multiple myeloma a contraindication to excretory urography because of the great possibility of producing transient to fatal renal failure. Others believe that the risk of causing anuria is definite but small. If excretory urography is performed in the presence of multiple myeloma, dehydration should be avoided since it favors protein precipitation in renal tubules. Because of the possibility of temporary suppression of urine, it is wise to allow an interval of at least 48 hours before excretory urography is repeated in patients with unilateral or bilateral reduction of normal renal function.

tion of normal renal function.

Adverse Reactions: See Section on General Adverse Reactions.

Intravenous Dosage Dosage and Administration

Adults. A dose of 30 to 60 ml. produces excellent shadows in the majority of adults subjected to partial dehydration and effective purgation. In persons of slight build, 20 ml. produces adequate shadows. For best results and minimal reactions, the total 30 to 60 ml. should be injected in one to three minutes and compression may be used. A small intravenous test dose may be administered as a possible aid in determining sensitivity to the medium. (See

General Precautions.)

Children. The suggested dosage for children up to 12 years old is presented in the table below. Children older than 12 years may be given an adult dose

Pediatric Dosage for Excretory Urography

Age	Body Weight	Dosage	
Under 2 years	up to 10 lbs.	5 to 10 ml.	
	10 to 30 lbs.	10 to 15 ml	
2 to 12 years	30 to 60 lbs.	15 to 30 ml.	
	over 60 lbs.	30 ml.	

Preliminary Preparation of Patient

Preliminary Preparation of Patient
Although clear shadows are often seen in patients who have had no preliminary preparation for urography, the largest percentage of satisfactory films is obtained in patients who abstain from fluids for 12 to 15 hours before the intravenous injection so that partial dehydration results. Unless contraindicated, a laxative may be taken at bedtime to eliminate gas from the intestine.

It is not advised that infants or young children abstain from fluids 12 to 15 hours prior to this examination because the injection of Hypaque meglumine 60 per cent (brand of meglumine diatrizoate) may represent an osmotic load superimposed upon the increased serum osmolarity obtained by partial dehydration.

\*\*Reentgenographic Technique\*\*

Roentgenographic Technique

Roentgenographic Technique

A preliminary scout film may be obtained before the intravenous injection. Excellent shadows can often be obtained immediately after administration of the radiopaque medium (within a five-minute period). If preliminary preparation has been carried out, the urinary organs are usually best visualized on films exposed 5, 10, or 15 minutes after intravenous injection. If a film of the bladder is required, it is generally taken 25 or 35 minutes after injection. In patients with impaired renal function, the best shadows may not be obtainable until later (30 minutes or more) because of delayed excretion, and additional film may have to be exposed. Most urologists and roentgenologists believe that compression immediately above the symphysis (obtained by application of a small hollow rubber ball about the size of a grapefruit or by the rolled bed sheet technique) assures adequate filling of the pelves and ureters, and hence is of great value. Although compression undoubtedly improves the urogram, it also seems to increase the possibility of pyelorenal backflow or reflux by raising the pressure within the urinary tract. within the urinary tract.

HOW SUPPLIED

Ampuls of 30 ml., boxes of 1, 10, and 25.
A 1 ml. sensitivity test ampul is furnished with each ampul.
Vials of 20 and 30 ml., rubber stoppered, boxes of 1, 10, and 25.
Vials of 50 ml., rubber stoppered, boxes of 1 and 10. Each vial contains sufficient excess to permit withdrawal of 1 ml.

Each vial contains sufficient excess to permit witndrawal or 1 mi, for testing sensitivity.

The 60 per cent solution contains calcium disodium edetate 1:10,000 as a sequestering stabilizing agent. Each 1 ml. contains approximately 282 mg. of organically-bound iodine. The viscosity of the solution is 6.17 cps at 25°C. and 4.12 cps at 37°C.



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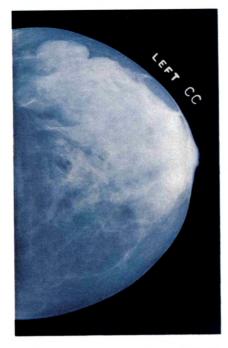
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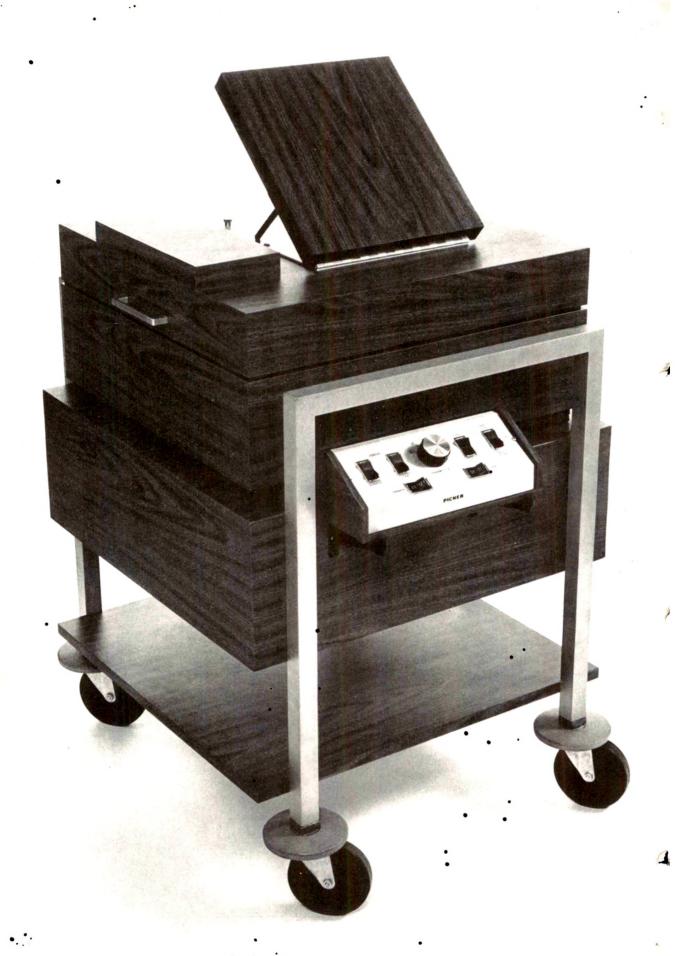


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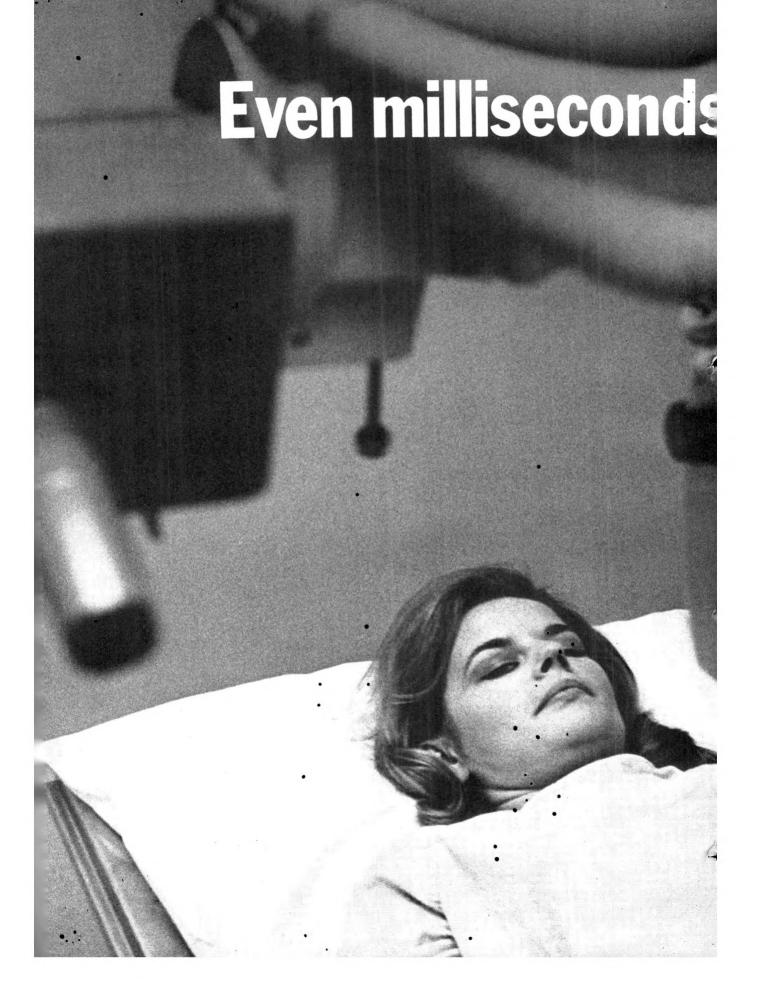
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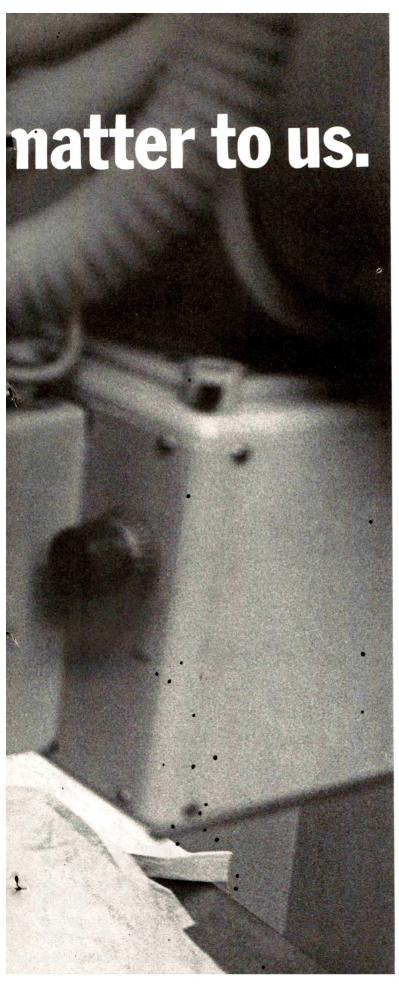
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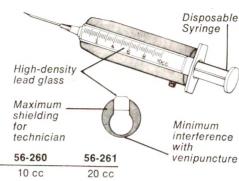


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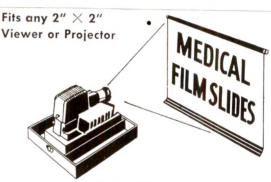
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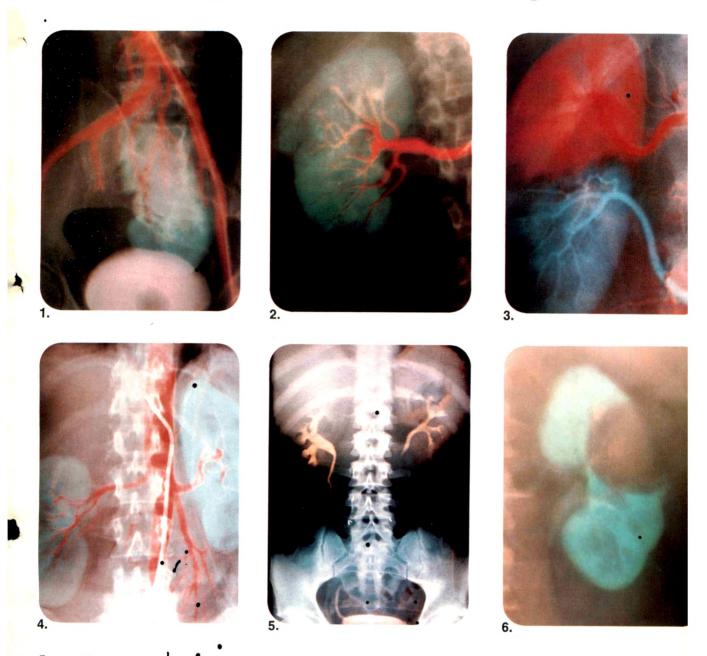
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### **EXCRETORY UROGRAPHY AND** DRIP INFUSION PYELOGRAPHY

... 71

**Description:** Hypaque sodium is sodium 3,5-diacetamido-2,4,6-triiodobenzoate, a radiopaque medium used to delineate internal structures. Hypaque sodium 50 per cent contains 300 mg. iodine per ml. Contains calcium disodium edetate 1:10,000 as stabilizer. NazCo3, NaOH, and HCl added to adjust pH between 6.5 and 7.5. Not for multiple dose use. Should be protected from strong light.

Warning: Do not use Hypaque sodium for myelography. Injection of even a small amount into the subarachnoid space may produce convulsions and result in fatality.

General and Specific Precautions: Caution is advised in patients with a history of bronchial asthma, other allergic manifestations, or of sensitivity to iodine; these conditions represent a special risk, though not an absolute contraindication. To avoid or minimize possible allergic reactions, premedication with antihistamines may be considered. Benadryl® (brand of diphenhydramine hydrochloride) in the same syringe with Hypaque may result in precipitation. A test dose of contrast medium is not entirely reliable. Severe reactions, including fatalities, have occurred with a test dose as well as with the full diagnostic dose.

Caution is advised in patients with severe cardiovascular disease. In patients with impaired renal function and cardiovascular disease, drip infusion pyelography imposes a sudden osmotic and sodium load which can precipitate congestive heart failure. Contrast media injected into arteries or veins can promote sickling of red cells in susceptible individuals. In patients with reduced renal function, repeat of excretory or retrograde pyelography should be delayed at least 48 hours to avoid temporary suppression of urine. In preparation for excretory urography of patients with multiple myeloma, partial dehydration is not recommended, since this may predispose to the precipitation of myeloma protein in the kidney tubules. When thyroid function studies (PBI and 24-hour radioiodine uptake levels) are indicated, they should be performed prior to radiographic studies or several days afterwards, to avoid inaccurate results. avoid inaccurate results

General and Specific Adverse Reactions: Adverse reactions, usually of a minor nature, have occurred in 10-14 per cent of patients who have received Hypaque intravenously. Reactions due to faulty technique nclude hematomas and ecchymoses, following extravasation from the rein, and pyrogenic reactions. Hemodynamic reactions include vaso-dilatation with flushing, hypotension and, rarely, vein cramp or thromophlebitis. Serious cardiovascular reactions include rare cases of cardiac arrest. Transient proteinuria may occur occasionally following the injection of radiopaques and, rarely, oliguria and anuria have been reported eccondary to a hypotensive reaction. Allergic reactions include asthmatic attacks, nasal and conjunctival symptoms, cutaneous reactions such as stricaria and, rarely, anaphylactic shock, sometimes with fatal outcome. Severe reactions may also be manifested by signs and symptoms elating to the respiratory system (dyspnea, cyanosis, pulmonary or arryngeal edema), or to the nervous system (restlessness, confusion, or convulsions). Other reactions include nausea, vomiting, excessive saltation, anxiety, headache, and dizziness. Infrequently, "iodism" (salivary gland swelling) from organic compounds appears two days after exposure and subsides by the sixth day. Reactions to drip infusion pyelogaphy may not appear until some hours after the examination.

### **ANGIOGRAPHY (PERIPHERAL ARTERIOGRAPHY** AND VENOGRAPHY)

Precautions (See also General Precautions): Extreme caution is advised n considering peripheral arteriography in patients suspected of having hromboangiitis obliterans (Buerger's disease). Any procedure (even seedling or insertion of a catheter) may induce a severe arterial and/or renous spasm. Caution is also advisable in patients with severe ischuma associated with ascending infection. mia associated with ascending infection.

Ima associated with ascending infection.

In addition to hose listed under General Adverse Reactions, are those due to arterial rauma during the procedure (i.e., needling, insertion of catheter, subntimal injection, perforation, etc.) as well as to the hypertonicity or ffect of the medium; also reported are transient arterial spasm, extrasation, hemorrhage, hematoma with tamponade, injury to nerves roximal to artery, thrombosis (rare in venography, if vein is irrigated ollowing injection), dissecting aneurysm, arteriovenous fisture, vith accidental perforation of femoral artery and vein during needlingly, ransient leg pain from contraction of calf muscles in femoral arteriogaphy; transient hypotension after intraarterial (brachial) injection, and rachial plexus injury with axillary artery injections. rachial plexus injury with axillary artery injections.

### EREBRAL ANGIOGRAPHY

nasmuch as cerebral angiography is a highly specialized procedure re-uiring the use of special techniques, it is recommended that Hypaque odium (brand of sodium diatrizoate) be used for this purpose only by ersons skilled and experienced in carrying out the procedure.

ontraindication: Carotid angiography should be avoided during the rogressive period of a stroke because of the increased risk of cerebral omplications.

recautions (See also General Precautions): Select patients for this pro-edure with care. Use the 50 per cent solution with caution in extreme enility (but not old age per se), advanced arteriosclerosis, severe hyertension, and cardiac decompensation.

he diagnostic value of the procedure, according to many authorities, then employed early enough in locating lesions amenable to surgery, any outweigh the added risk to patients who have recently experienced erebral embolism or thrombosis (stroke syndrome). A small number of

postangiographic fatalities, including progressive thrombosis, have occurred in which the procedure did not appear to play a role. Patients with severe cerebrovascular disease may be examined primarily by indirect methods of angiography.

Care should be exercised to avoid contaminating catheters, syringes, needles, and contrast media with glove powder or cotton fibers.

Angiography is hazardous in subarachnoid hemorrhage. In migraine, the procedure can be hazardous because of ischemic complications, particularly if performed during or soon after an attack.

Adverse Reactions (See also General Adverse Reactions): The major sources of complications are faulty technique, occlusive atherosclerotic vascular disease, repeated injections of the contrast media, and higher doses than those recommended.

Untoward reactions are mostly mild and transient, although permanent visual field defects and deaths have been reported.

Vascular reactions: flushing, vessel spasm, thrombophlebitis, and cutaneous petechiae.

Neurologic complications: transient cerebral blindness, neuromuscular disorders, convulsions, coma, hemiparesis, unilateral dysesthesias, visual field defects, aphasia, and respiratory difficulties.

### **AORTOGRAPHY**

Precautions (See also General Precautions): Special caution is advised to avoid inadvertent intrathecal injection when using the translumbar technique. The incidence and severity of reactions or complications that may occur are influenced by: the care and experience with which the procedure is performed; the amount and type of medium used; the age and condition of the patient; and the premedication and anesthesia used. Since aortography is not without some danger, it should be performed only by those experienced in the technique. Wherever possible, repeated injections of the solution during a single study should be avoided.

Adverse Reactions (See also General Adverse Reactions): Renal damage and shutdown; neurologic complications such as transverse myelitis or paraplegia; cardiovascular complications such as shock, cardiac arrest or failure, coronary occlusion, arterial thrombosis, embolism, and perforation of vessels; extravasation or hemorrhage from the puncture site or retroperitioneal catheter perforation; necrosis of the intestinal wall; acute pancreatitis; deaths; diffuse cutaneous petechiae; subintimal injection and aortic dissection.

### INTRAOSSEOUS VENOGRAPHY

See General Precautions and Adverse Reactions. A general anesthetic is sometimes necessary since the method is painful. Occasionally, extravasation of the contrast medium from the needle into the soft tissue

### DIRECT CHOLANGIOGRAPHY

**Precaution** (See also General Precautions): This procedure should be used with caution in the presence of acute pancreatitis, injecting no more than 5 to 10 ml. without undue pressure.

Adverse Reactions (See also General Adverse Reactions): These may be attributed to injection pressure or excessive volume of the medium, resulting in overdistention. Such pressure may produce a sensation of epigastric fullness, followed by moderate pain in the back or right upper abdominal quadrant, which will subside when injection is stopped.

Some of the medium may enter the pancreatic duct and cause a transient serum amylase elevation 6 to 18 hours later, without apparent ill effects. Pancholangitis resulting in liver abscess has been reported. Occasionally, nausea, vomiting, fever, and tachycardia have been observed.

### **HYSTEROSALPINGOGRAPHY**

Contraindications: Menstruation, active or imminent; infection in any part of the genital tract, including the external genitalia; pregnancy, known or suspected. Use not advised for six months after end of pregnancy, or 30 days after conization or curettement.

**Precaution** (See also General Precautions): Caution should be exercised in patients with known or suspected carcinoma to avoid possible spread of the lesion by the procedure.

### **SPLENOPORTOGRAPHY**

Precautions (See also General Precautions): Procedure should be performed with caution on patients with blood dyscrasias, a tendency to severe bleeding, or a spleen recently become tender and palpable.

Adverse Reactions (See also General Adverse Reactions): Persistent hemorrhage with hemoperitoneum has been reported, and, in some instances, hemorrhage has required splenectomy.

**How Supplied:** Ampuls of 30 ml., boxes of 10 and 25. Boxes of 25-1 ml. ampuls for testing sensitivity are available upon request. Vials of 20 and 30 ml., rubber stoppered, boxes of 10 and 25. Vials of 50 ml., rubber stoppered, boxes of 10. Each vial contains sufficient excess to permit withdrawal of 1 ml. for testing sensitivity.

If the solution is chilled, crystals may form but will readily dissolve if the ampul or vial is placed in moderately hot water before use. Cool to body temperature before injecting.





### From nipple to chest wall:



### Only one specialized radiographic mammography system actually pictures the entire breast—the Picker Mammorex.

Incredible but true: Mammorex is the only such specialized system that shows the entire breast all the way back to and including the retromammary space. Since malignancy shows no geographic preference, neither does Mammorex. Not so with competitive equipment: lesions proximal to the chest wall are just not visible.

Though this is reason enough to choose Mammorex over other specialized radiographic mammography equipment, there are others. But why choose a *specialized* system in the first place? The superiority of a specialized system over general purpose equipment— and the superiority of Mammorex over other specialized equipment— are discussed briefly below. We urge that you review this material and then ask your Picker representative for detailed information on the finest mammography unit for facilitating early cancer diagnosis: Mammorex.

### **Superior Diagnostic Information**

Mammorex, and *only* Mammorex, consistently shows the *entire* breast, shows it in *every* position, and shows it in a way which maximizes the possibility of seeing the smallest lesions.

### Visualization of Entire Breast

Competitive specialized equipment fails to show the rib cage. Mammorex shows the chest wall assuring visibility of the entire breast.

### All Views Possible

Reclining views cannot be made with competitive specialized equipment.

Mammorex permits all views including those in the reclining position.

### Superb Image Quality

Superior image quality results from a special x-ray tube and a breast compression device. X-ray tube: this special molybdenum target tube is singularly appropriate for mammography since it efficiently generates the radiation spectrum specifically required for the desired contrast and detail. Also, this tube's construction permits a superior geometry which yields better resolution and reduction in undesirable magnification as compared to competitive equipment. Breast Compressor: Breast compression—not achievable with general purpose equipment—reduces breast thickness (and motion) and hence increases the likelihood of detecting small lesions.

### Improved Patient Comfort and Ease of Use •

Mammorex is an isocentric system that minimizes patient moving, rotating, and shifting —and shortens examination time. And since Mammorex has been specifically designed to do one job and to do it well, the time and annoyance of preparing general purpose equipment for mammography is eliminated.

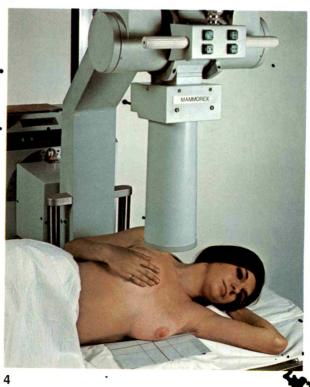


- 1 Caniocaudad view2 Mediolateral view3 Axillary view4 Reclining view





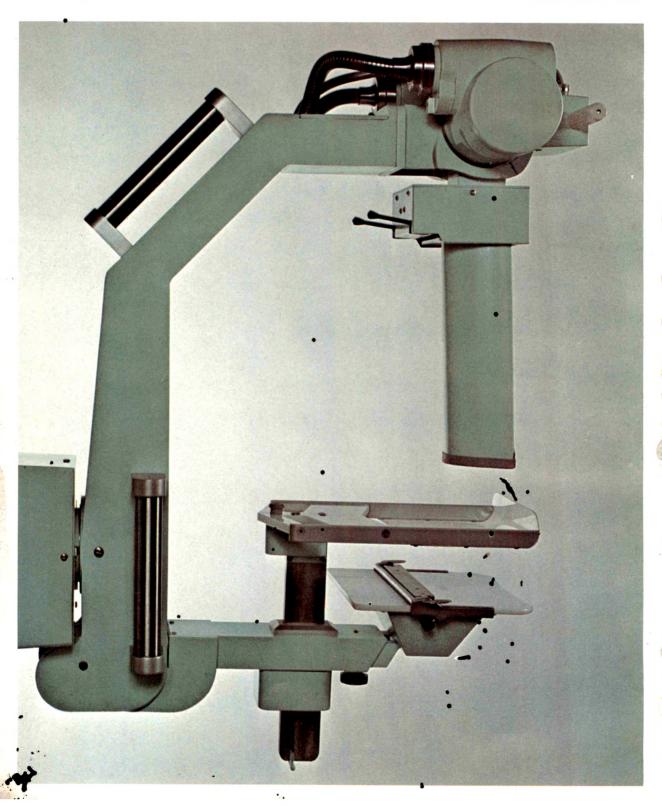




### Canclusion

For mammography that pictures *the entire scene* and does so with the highest diagnostic quality, for mammography that's easy on the patient and is easy to do—for mammography that truly facilitates confident diagnosis—consider Mammorex. To do so: merely contact your local Picker representative or write Picker Corporation, 595 Miner Road, Cleveland, Ohio 44143.

### **PICKER**







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# The finest system for mammography is described in this issue:

## The Picker Mammorex.

(Another major contribution from Picker.)

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